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(54) Title: RHO-KINASE INHIBITORS

(57) Abstract: Disclosed are compounds and derivatives thereof, their synthesis, and their use as Rho-kinase inhibitors. These compounds are useful for inhibiting tumor growth, treating erectile dysfunction, and treating other indications mediated by Rho-kinase, e.g., coronary heart disease.

Rho-Kinase Inhibitors

Field of the Invention

The present invention relates to compounds and derivatives thereof, their synthesis, and their use as Rho-kinase inhibitors. These compounds of the present invention are useful for inhibiting tumor growth, treating erectile dysfunction, and treating other indications mediated by Rho-kinase, e.g., coronary heart disease.

Background

The pathology of a number of human and animal diseases including hypertension, erectile dysfunction, coronary cerebral circulatory impairments, neurodegenerative disorders and cancer can be linked directly to changes in the actin cytoskeleton. These diseases pose a serious unmet medical need. The actin cytoskeleton is composed of a meshwork of actin filaments and actin-binding proteins found in all eukaryotic cells. In smooth muscle cells the assembly and disassembly of the actin cytoskeleton is the primary motor force responsible for smooth muscle contraction and relaxation. In non-muscle cells, dynamic rearrangements of the actin cytoskeleton are responsible for regulating cell morphology, cell motility, actin stress fiber formation, cell adhesion and specialized cellular functions such as neurite retraction, phagocytosis or cytokinesis (Van Aelst, et al. *Genes Dev* **1997**, *11*, 2295).

The actin cytoskeleton is controlled by a family of proteins that are a subset of the Ras superfamily of GTPases. This subset currently consists of RhoA through E and RhoG (refereed to collectively as Rho), Rac 1 and 2, Cdc42Hs and G25K and TC10 isoforms (Mackay, et al. *J Biol Chem* **1998**, *273*, 20685). These proteins are GTP (guanine nucleotide triphosphate) binding proteins with intrinsic GTPase activity. They act as molecular switches and cycles between inactive GDP (guanine nucleotide diphosphate) bound and active GTP bound states. Using biochemical and genetic manipulations, it has been possible to assign functions to each family member. Upon activation the Rho proteins controls the formation of actin stress fibers, thick bundles of actin filaments, and the clustering of integrins at focal adhesion complexes. When activated the Rac proteins control the formation of lamellopodia or membrane ruffles on the cell surface and Cdc42 controls filopodia formation. Together this family of proteins plays a critical part in the control of key cellular functions including cell movement, axonal guidance, cytokinesis, and changes in cell morphology, shape and polarity.

Depending on the cell type and the activating receptor, the Rho proteins can control different biological responses. In smooth muscle cells, Rho proteins are responsible for the calcium sensitization during smooth muscle contraction. In non-smooth muscle cells the Rho GTPases are responsible for the cellular responses to agonist such as lysophosphatidic acid (LPA), thrombin and thromboxane A_2 (Fukata, et al. *Trends Pharcol Sci* **2001**, *22*, 32). Agonist response is coupled through heterotrimeric G proteins $G_{alpha12}$ or $G_{alpha13}$ (Goetzl, et al. *Cancer Res* **1999**, *59*, 4732; Buhl, et al. *J Biol Chem* **1995**, *270*, 24631) though other receptors may be involved. Upon activation Rho GTPases activate a number of downstream effectors including PIP5-kinase, Rhothekin, Rhophilin, PKN and Rho kinase isoforms ROCK-1/ROKbeta and ROCK-1/ROKalpha (Mackay and Hall *J Biol Chem* **1998**, *273*, 20685; Aspenstrom *Curr Opin Cell Biol* **1999**, *11*, 95; Amano, et al. *Exp Cell Res* **2000**, *261*, 44).

Rho kinase was identified as a RhoA interacting protein isolated from bovine brain (Matsui, et al. *Embo J* **1996**, *15*, 2208). It is a member of the myotonic dystrophy family of protein kinase and contains a serine/threonine kinase domain at the amino terminus, a coiled-coil domain in the central region and a Rho interaction domain at the carboxy terminus (Amano, et al. *Exp Cell Res* **2000**, *261*, 44). Its kinase activity is enhanced upon binding to GTP-bound RhoA and when introduced into cells, it can reproduce many of the activities of activated RhoA. In smooth muscle cells Rho kinase mediates calcium sensitization and smooth muscle contraction and inhibition of Rho kinase blocks 5-HT and phenylephrine agonist induced muscle contraction. When introduced into non-smooth muscle cells, Rho kinase induces stress fiber formation and is required for the cellular transformation mediated by RhoA (Sahai, et al. *Curr Biol* **1999**, *9*, 136). Rho kinase regulates a number of downstream proteins through phosphorylation, including myosin light chain (Somlyo, et al. *J Physiol (Lond)* **2000**, *522 Pt 2*, 177), the myosin light chain phosphatase binding subunit (Fukata, et al. *J Cell Biol* **1998**, *141*, 409) and LIM-kinase 2 (Sumi, et al. *J Bio Chem* **2001**, *276*, 670).

Inhibition of Rho kinase activity in animal models has demonstrated a number of benefits of Rho kinase inhibitors for the treatment of human diseases. Several patents have appeared claiming (+)-trans-4-(1-aminoethyl)-1-(pyridin-4-ylaminocarbonyl)cyclohexane dihydrochloride monohydrate (WO-00078351, WO-00057913) and substituted isoquinolinesulfonyl (EP-00187371) compounds as Rho kinase inhibitors with activity in animal models. These include models of cardiovascular diseases such as hypertension (Uehata, et al.

Nature **1997**, *389*, 990), atherosclerosis (Retzer, et al. *FEBS Lett* **2000**, *466*, 70), restenosis (Eto, et al. *Am J Physiol Heart Circ Physiol* **2000**, *278*, H1744; Negoro, et al. *Biochem Biophys Res Commun* **1999**, *262*, 211), cerebral ischemia (Uehata, et al. *Nature* **1997**, *389*, 990; Seasholtz, et al. *Circ Res* **1999**, *84*, 1186; Hitomi, et al. *Life Sci* **2000**, *67*, 1929; Yamamoto, et al. *J Cardiovasc Pharmacol* **2000**, *35*, 203), cerebral vasospasm (Sato, et al. *Circ Res* **2000**, *87*, 195; Kim, et al. *Neurosurgery* **2000**, *46*, 440), penile erectile dysfunction (Chitaley, et al. *Nat Med* **2001**, *7*, 119), central nervous system disorders such as neuronal degeneration and spinal cord injury (Hara, et al. *J Neurosurg* **2000**, *93*, 94; Toshima, et al. *Stroke* **2000**, *31*, 2245) and in neoplasias where inhibition of Rho kinase has been shown to inhibit tumor cell growth and metastasis (Itoh, et al. *Nat Med* **1999**, *5*, 221; Somlyo, et al. *Biochem Biophys Res Commun* **2000**, *269*, 652), angiogenesis (Uchida, et al. *Biochem Biophys Res Commun* **2000**, *269*, 633; Gingras, et al. *Biochem J* **2000**, *348 Pt 2*, 273), arterial thrombotic disorders such as platelet aggregation (Klages, et al. *J Cell Biol* **1999**, *144*, 745; Retzer, et al. *Cell Signal* **2000**, *12*, 645) and leukocyte aggregation (Kawaguchi, et al. *Eur J Pharmacol* **2000**, *403*, 203; Sanchez-Madrid, et al. *Embo J* **1999**, *18*, 501), asthma (Setoguchi, et al. *Br J Pharmacol* **2001**, *132*, 111; Nakahara, et al. *Eur J Pharmacol* **2000**, *389*, 103), regulation of intraoccular pressure (Honjo, et al. *Invest Ophthalmol Vis Sci* **2001**, *42*, 137) and bone resorption (Chellaiah, et al. *J Biol Chem* **2000**, *275*, 11993; Zhang, et al. *J Cell Sci* **1995**, *108*, 2285).

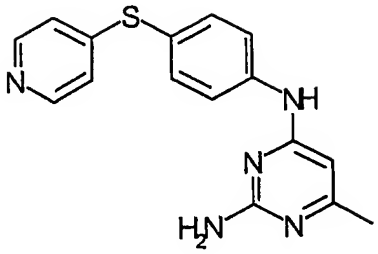
The inhibition of Rho kinase activity in patients has benefits for controlling cerebral vasospasms and ischemia following subarachnoid hemorrhage (*Pharma Japan* **1995**, *1470*, 16).

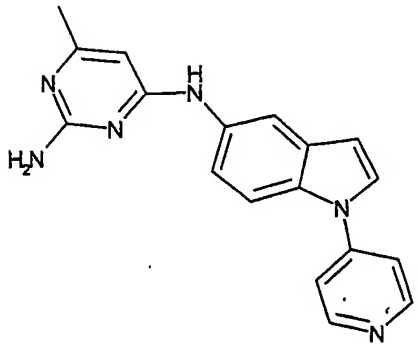
Summary of the Invention

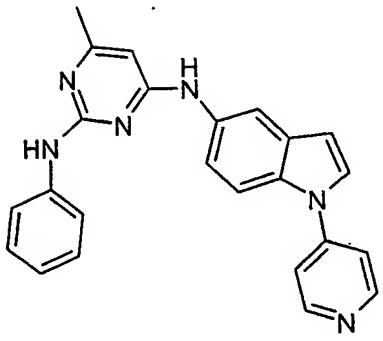
The compounds and their derivatives presented in this invention are useful as Rho Kinase inhibitors and thus have utilities in the treatment of hypertension, atherosclerosis, restenosis, cerebral ischemia, cerebral vasospasm, neuronal degeneration, spinal cord injury, cancers of the breast, colon, prostate, ovaries, brain and lung and their metastases, thrombotic disorders, asthma, glaucoma and osteoporosis.

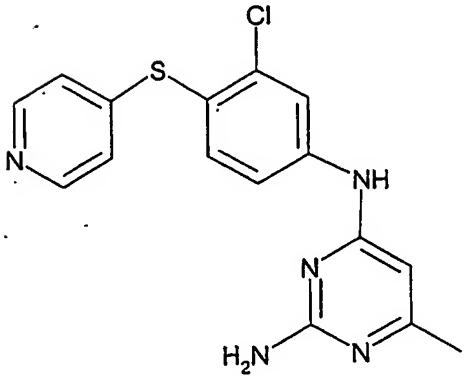
In addition, the compounds of the invention are useful to treat erectile dysfunction, i.e., erectile dysfunction mediated by Rho-kinase. Erectile dysfunction can be defined as an inability to obtain or sustain an erection adequate for intercourse, WO 94/28902, U.S.P. 6,103,765 and U.S.P. 6,124,461.

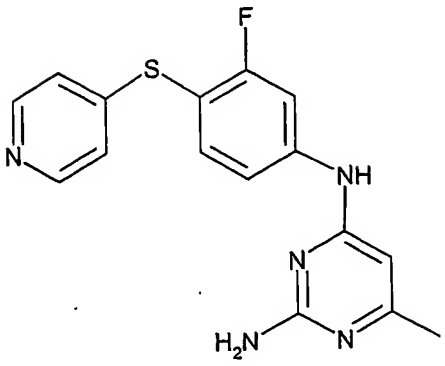
The invention involves compounds of the following structures:

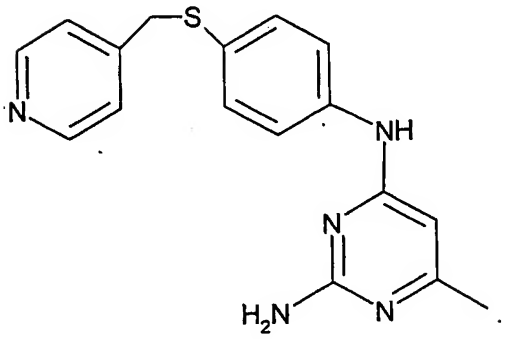


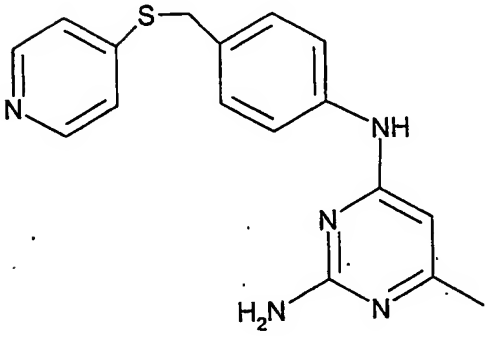


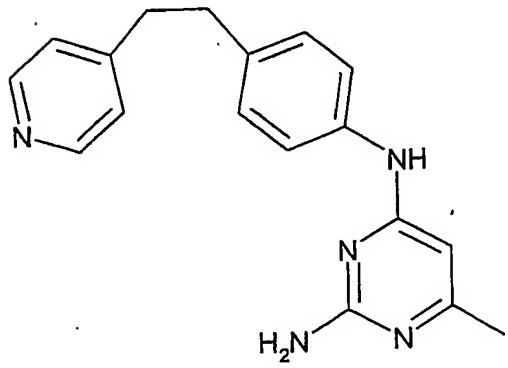


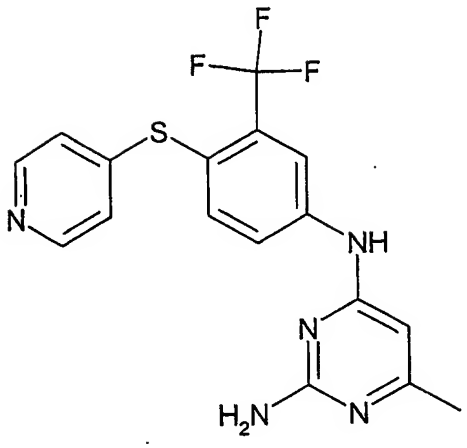


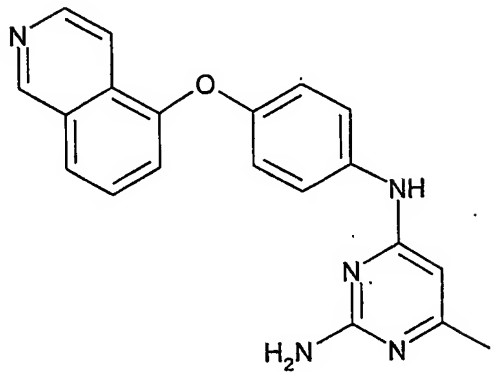


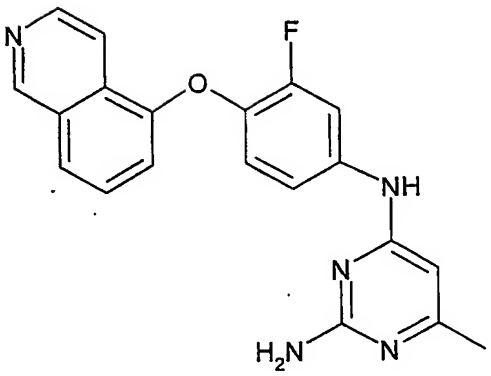


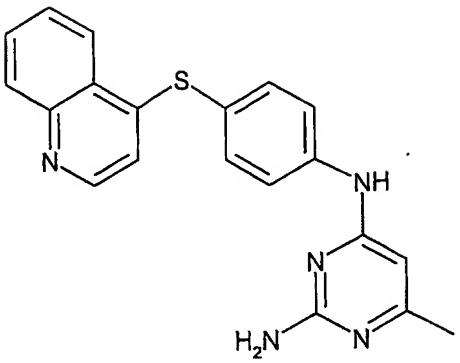


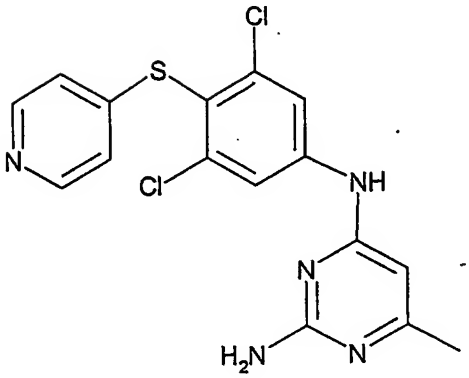


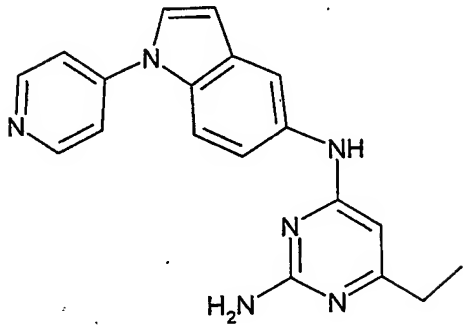


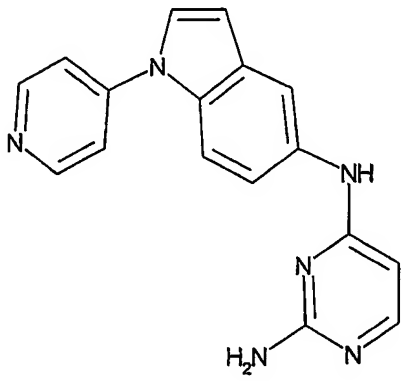


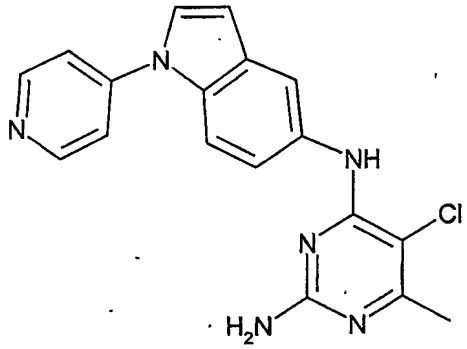


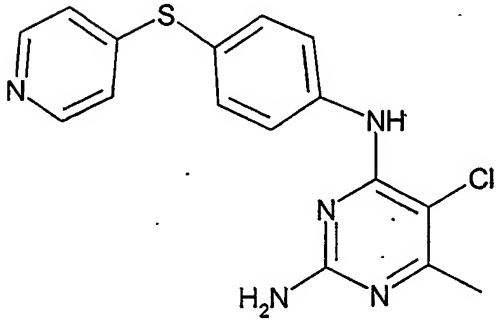


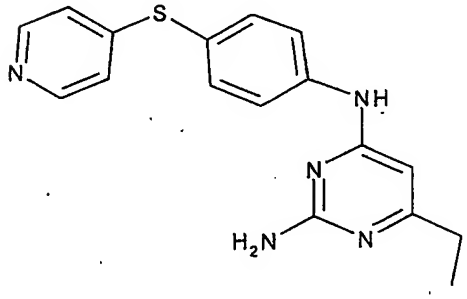


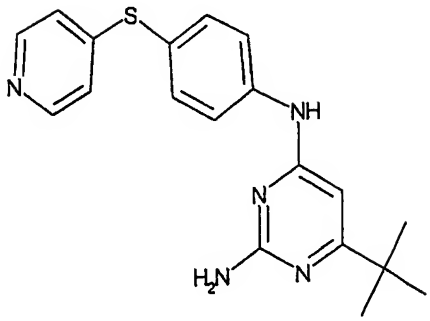


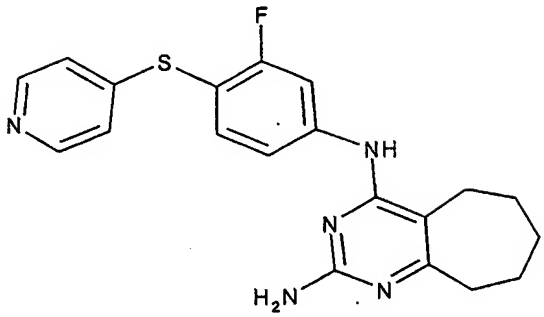


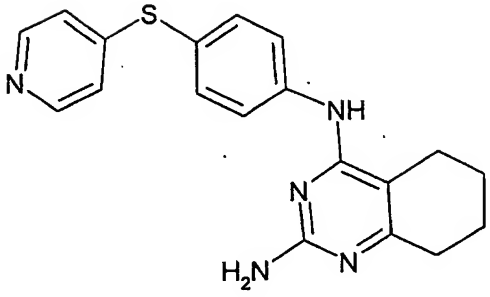


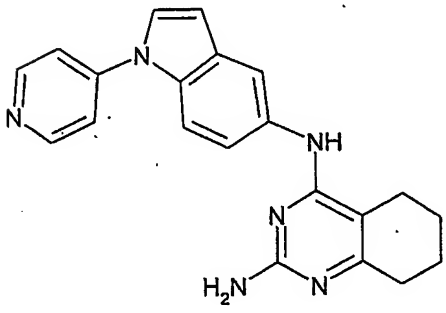


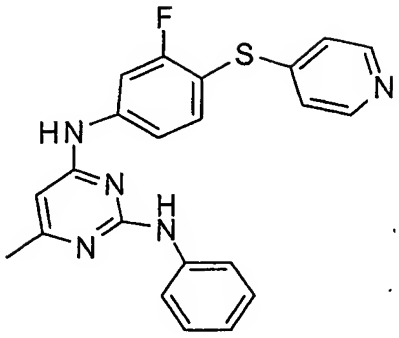


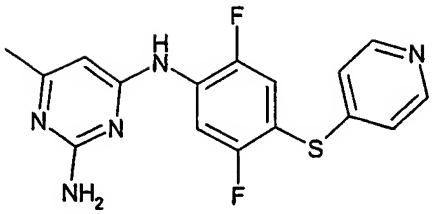


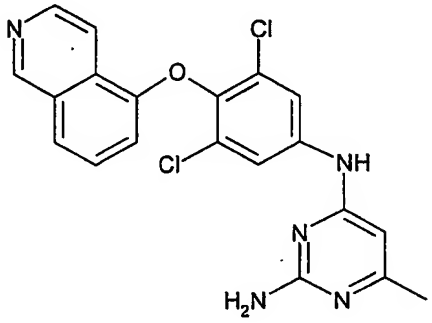


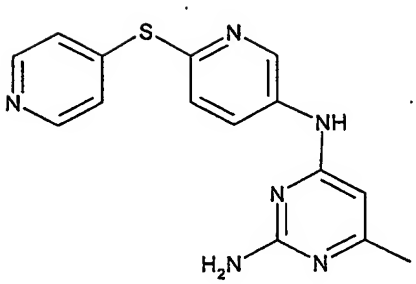


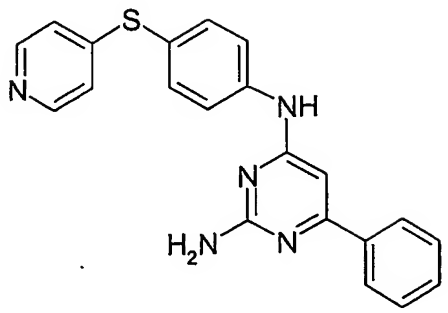


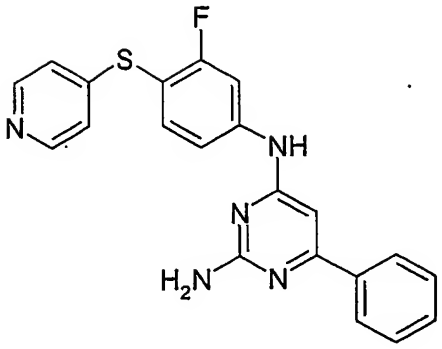


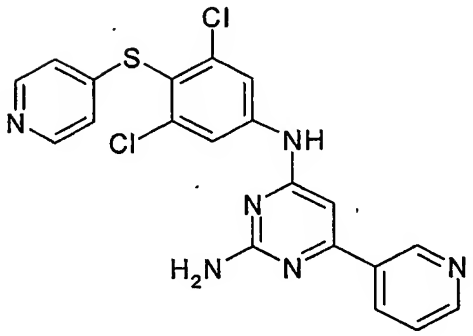


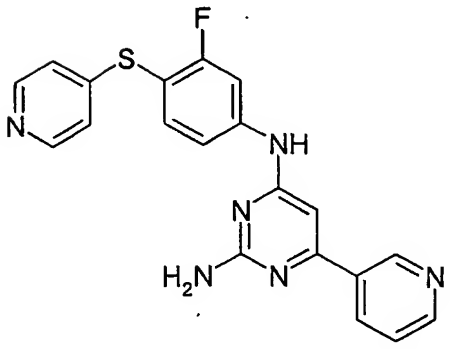


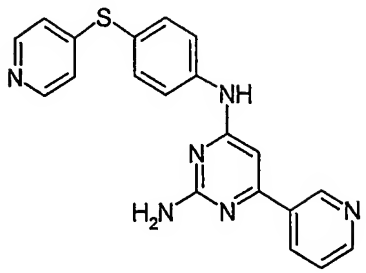


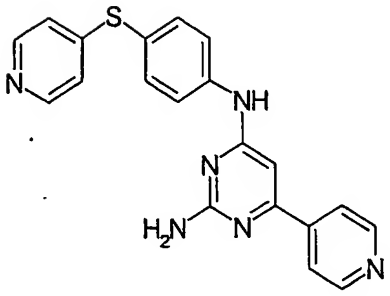


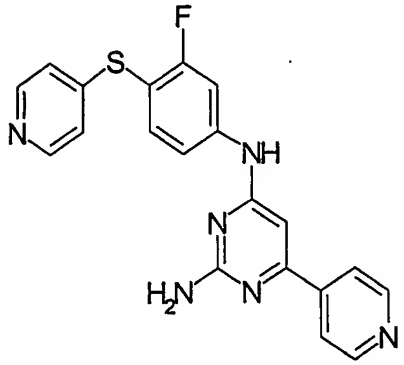


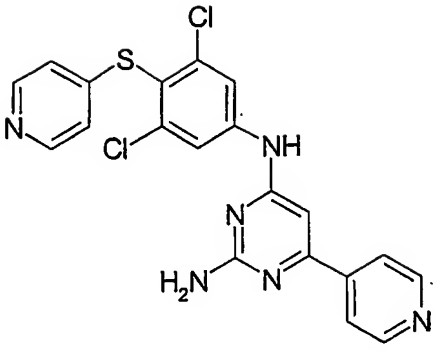


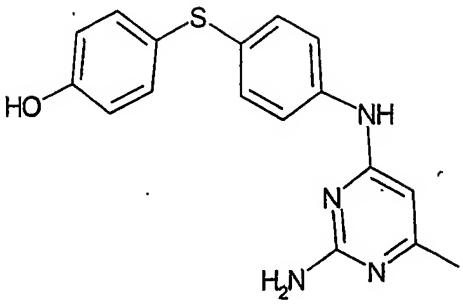


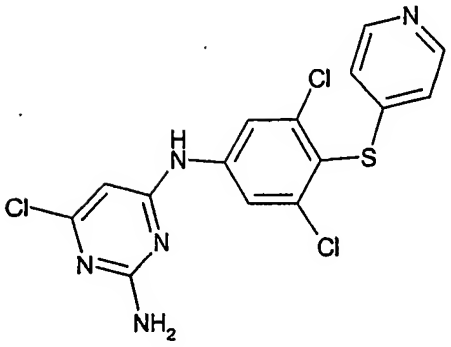


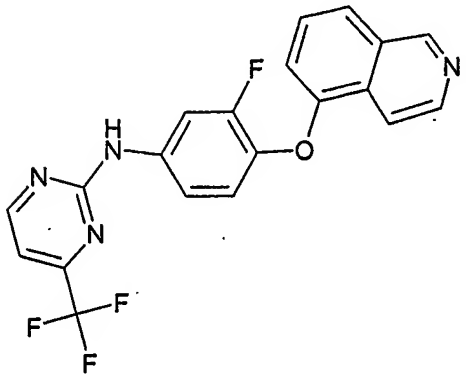


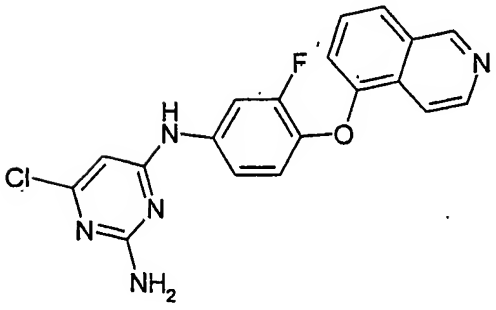


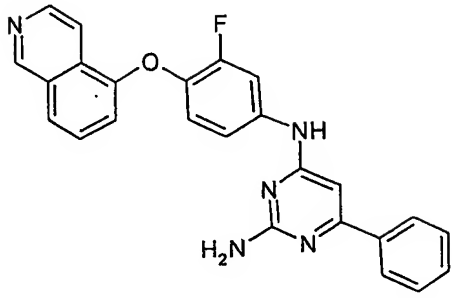


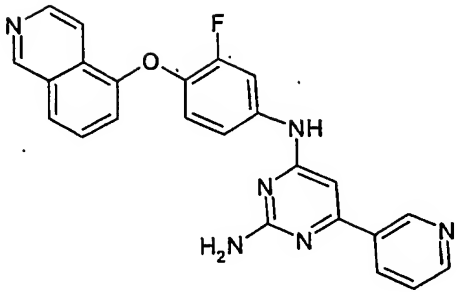


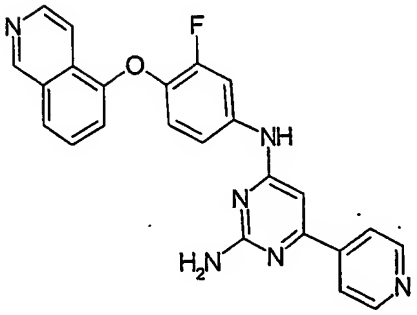


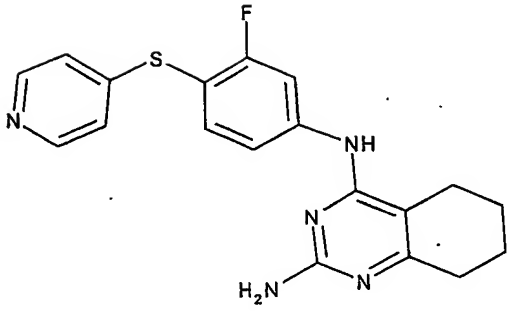


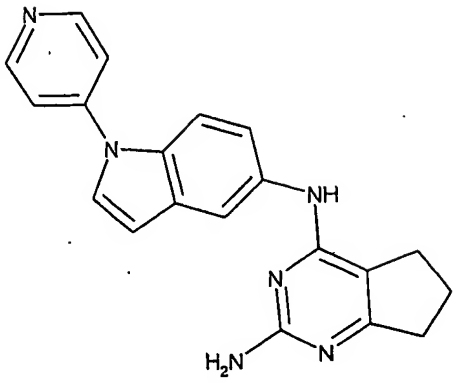


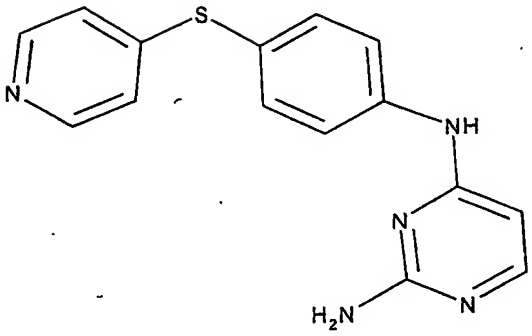


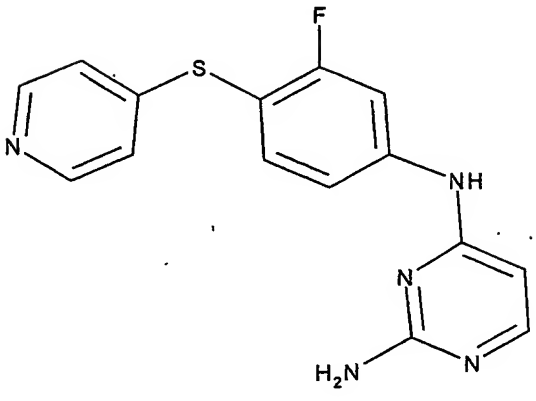


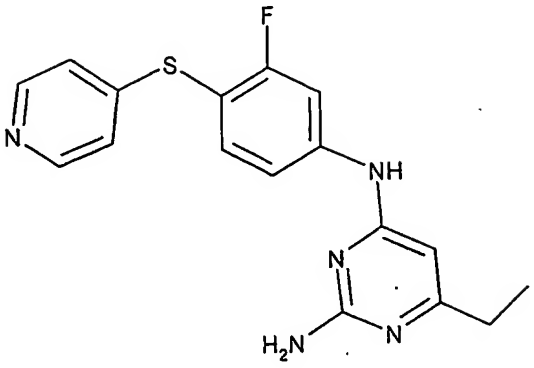


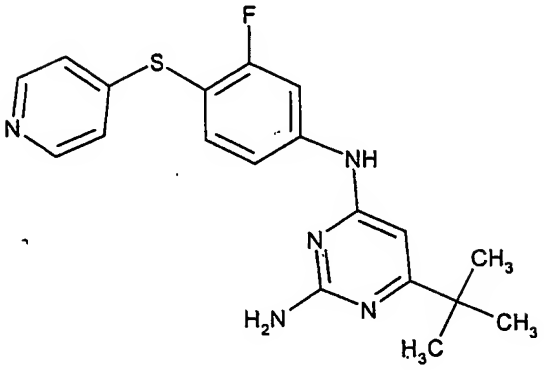












The compounds of the Formula I can be made according to routine, conventional chemical methods, and/or as disclosed below, from starting materials which are either commercially available or producible according to routine, conventional chemical methods. Methods for the preparation of the compounds are given below in the Examples.

In the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

The entire disclosure of all applications, patents and publications, cited above or below, and Provisional Application No. 60/349,986, filed January 23, 2002, are hereby incorporated by reference.

Abbreviations and Acronyms

When the following abbreviations are used herein, they have the following meaning:

Ac_2O	acetic anhydride
anhy	anhydrous
n-BuOH	*n*-butanol
t-BuOH	*t*-butanol
CD_3OD	methanol-d_4
Celite®	diatomaceous earth filter agent, ® Celite Corp.
CH_2Cl_2	methylene chloride
CI-MS	chemical ionization mass spectroscopy
conc	concentrated
dec	decomposition
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ELSD	evaporative light scattering detector
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
HPLC ES-MS	high performance liquid chromatography-electrospray mass spectroscopy
NMM	4-methylmorpholine
Ph_3P	triphenylphosphine
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	palladium acetate
$P(O)Cl_3$	phosphorous oxychloride

RT	retention time (HPLC0)
rt	room temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography

Experimental Examples

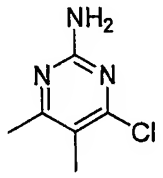
All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. Thin layer chromatography (TLC) was performed on Analtech UNIPLATE ™ pre-coated glass-backed silica gel 60 A F-254 250 μm plates. Column chromatography (flash chromatography) was performed on a Biotage system using 32-63 micron, 60 A, silica gel pre-packed cartridges. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were measured with a Varian (300 MHz) spectrometer with residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Low-resolution mass spectra (MS) were either obtained as electron impact (EI) mass spectra or as fast atom bombardment (FAB) mass spectra.

The IUPAC name was obtained using the ACD/ILab Web service.

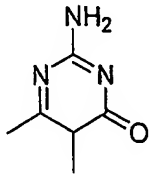
A. Preparation of chloropyrimidine intermediates

Intermediate A1

Preparation of 2-amino-4-chloro-5,6-dimethyl-pyrimidine

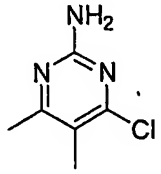


Step 1. Preparation of 2-amino-5,6-dimethyl-4-pyrimidinone



To a solution of ethyl 2-acetoacetate (6.0 g, 41.6 mmol) and guanidine carbonate (5.6 g, 31.2 mmol) in EtOH (32 mL) was added 12 N HCl (350 μL). The mixture was refluxed for 16 h. After the reaction was cooled to room temperature, the solid was collected by filtration and washed with EtOH. A solution of the solid in 1 N NaOH was refluxed for 3 h. After the reaction was cooled to room temperature, the aqueous mixture was adjusted to pH = 5 with concentrated acetic acid. The resulting precipitate was collected by filtration, washed with water and then with hexanes, and dried under vacuum. Desired compound (6.34 g, 45.6 mmol; 100% yield); ^{1}H NMR (D_2O; NaOD) δ 1.47 (s, 3H), 1.29-1.30 (m, 2H), 1.22 (s, 3H); ES MS $[M+H]^+$= 140.

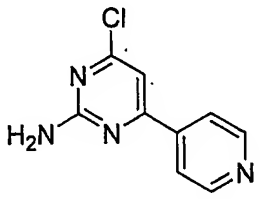
Step 2. Preparation of 2-amino-4-chloro-5,6-dimethyl-pyrimidine



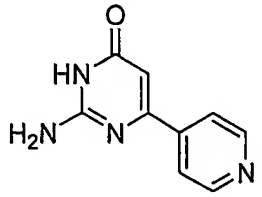
The product of the previous step (2.0 g, 14.4 mmol) and phosphorus oxychloride (6 mL, 57.5 mmol), was refluxed for 4 h. The reaction was cooled to rt and poured over ice. The mixture was separated and the aqueous layer was extracted with chloroform (3 x 75 mL). The aqueous mixture was adjusted to pH = 9 with concentrated ammonium hydroxide. The resulting solid product was collected by filtration, washed with water, and dried under vacuum. Desired compound (963 mg, 6.1 mmol; 43% yield); mp = 212 - 220°C; ES MS $[M+H]^+$= 158; TLC (CH_2Cl_2-MeOH, 90:10); R_f = 0.72.

Intermediate A2

Preparation of 2-amino-4-chloro-6-(4-pyridyl)pyrimidine

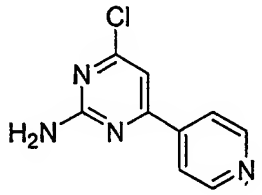


Step 1. Preparation of 2-amino-4-hydroxy-6-(4-pyridyl)pyrimidine



A solution of guanidine carbonate (7.1 g, 39 mmol, 1.5 eq), ethyl isonicotinoyl acetate (10 g, 51.76 mmol), and hydrochloric acid (0.75 mL, 9.0 mmol) in absolute ethanol (80 mL) was refluxed under argon overnight. The precipitate formed was filtered, washed with ethanol and dried. The solid was then dissolved in 1 N NaOH (100 mL) and refluxed for 2 h. The reaction mixture was then cooled to room temperature, acidified with glacial acetic acid, and the solid formed was filtered and dried to afford the desired product as a white solid (5.45 g, 56%). ^{1}H-NMR (DMSO-d_6) δ 6.24 (s, 1H), 6.79 (bs, 2H), 7.85 (d, J=5.1 Hz, 2H), 8.62 (d, J=5.3 Hz, 2H), 11.22 (bs, 1H).

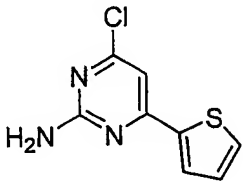
Step 2. Preparation of 2-amino-4-chloro-6-(4-pyridyl)pyrimidine :



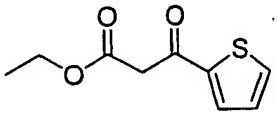
A solution of 2-amino-4-hydroxy-6-(4-pyridyl)pyrimidine (5.45 g, 29 mmol) in $POCl_3$ (12 mL) was refluxed under argon for 5 h. The reaction mixture was cooled to room temperature, poured over ice, and allowed to stir at room temperature for 2 h to ensure the quenching of $POCl_3$. At this time, the mixture was made basic upon addition of 1 N NaOH and the brown solid was filtered to afford 4.52 g of crude product, which was used without further purification (NMR analysis showed 1:1 product / starting material). The filtrate formed more solid upon standing at room temperature (1 g, NMR analysis showed 2:1 product / starting material). ^{1}H-NMR (DMSO-d_6) δ 7.34 (bs, 2H), 7.38 (s, 1H), 7.99 (d, J=4.2 Hz, 2H), 8.72 (d, J=4.6 Hz, 2H).

Intermediate A3

Preparation of 2-amino-4-chloro-6-(2-thienyl)pyrimidine

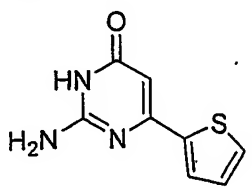


Step 1. Preparation of ethyl-2-(thiophene-2-oyl)acetate.



A solution of thiophene-2-carboxylic acid (8.9 g, 68.5 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (12.0 g, 81.6 mmol), and 4-dimethylaminopyridine (17.0 g, 138 mmol) in dry CH_2Cl_2 (100 mL) was cooled to 0 °C and treated with a solution of 1,3-dicyclohexylcarbodiimide (75 mL, 1.0 M in CH_2Cl_2, 75 mmol). The reaction was allowed to stir at room temperature for 2 h and the dicyclohexylurea was then filtered and washed with CH_2Cl_2. The filtrate was concentrated at reduced pressure and the residue was dissolved in absolute ethanol (400mL). The solution was then treated with a solution of *p*-toluenesulfonic acid monohydate (32 g, 168 mmol) in absolute ethanol (100 mL) and refluxed under argon for 1 h. At this time, the ethanol was removed at reduced pressure and the residue was dissolved in EtOAc and washed sequentially with H_2O (300 mL), saturated $NaHCO_3$ (200 mL), 1 N HCl (200 mL), saturated NaCl, and dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue was filtered through a pad of silica with 10% EtOAc/90% hexanes to afford the desired product as an oil (13 g, 96%). TLC (20% EtOAc/80% hexane) R_f 0.21; ^{1}H-NMR (DMSO-d_6) δ 1.17 (t, J=7.01, 3H), 4.06-4.14 (m, 4H), 7.25 (t, *J*=5.1 Hz, 1H), 7.98 (d, *J*=3.8 Hz, 1H), 8.06 (d, *J*=4.9 Hz, 1H).

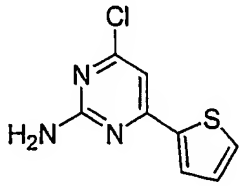
Step 2. Preparation of 2-amino-4-hydroxy-6-(2-thienyl)pyrimidine.



The procedure was similar to that used for Intermediate **A2**, step1,using ethyl-2-(thienyl-2-oyl)acetate as starting material. (43% yield). TLC (6% MeOH/94% CH_2Cl_2) R_f 0.23; MS ES

194 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 6.06 (s, 1H), 6.70 (bs, 2H), 7.11 (t, J=4.9 Hz, 1H), 7.64 (d, J=4.9 Hz, 1H), 7.70 (d, J=3.6 Hz, 1H), 10.95 (bs, 1H).

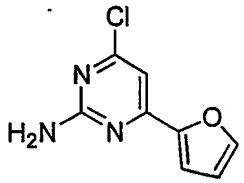
Step 3. Preparation of 2-amino-4-chloro-6-(2-thienyl)pyrimidine.



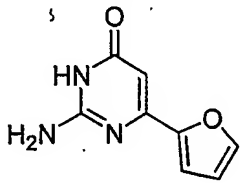
The procedure was similar to that of Intermediate **A2**, step 2, using 2-amino-4-hydroxy-6-(2-thiophene)pyrimidine as starting material .It afforded 33% yield after purification on silica with 15% EtOAc/85% hexanes. TLC (20% EtOAc/80% hexanes) R_f 0.29; ^{1}H-NMR (DMSO-d_6) δ 7.16-7.23 (m, 4H), 7.77 (dd, J=0.8, 5.0 Hz, 1H), 7.98 (dd, J=1.0, 3.8 Hz, 1H).

Intermediate A4

Preparation of 2-amino-4-chloro-6-(2-furyl)pyrimidine

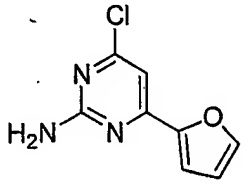


Step 1. Preparation of 2-amino-4-hydroxy-6-(2-furyl)pyrimidine.



The general procedure for the preparation of Intermediate **A2**, (step 1) was used ; (37% yield). MS (ES) 178 $[M+H]^+$.

Step 2. Preparation of 2-amino-4-chloro-6-(2-furyl)pyrimidine.

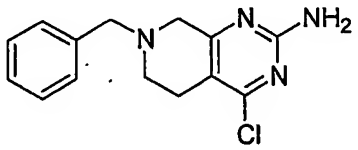


A solution of 2-amino-4-hydroxy-6-(2-furyl)pyrimidine (1.40 g, 7.9 mmol) in $POCl_3$ (4 mL) was refluxed under argon for 2 h. The $POCl_3$ was distilled; the residue was diluted with EtOAc and poured over iced saturated $NaHCO_3$. The layers were separated and the aqueous was

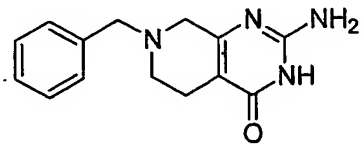
extracted with EtOAc (100 mL). The combined extracts was washed with saturated NaCl, dried ($MgSO_4$), and the solvent removed at reduced pressure to afford 0.5 g of crude product, which was used without further purification. TLC (20% EtOAc/80% hexane) R_f 0.26; ^{1}H-NMR (DMSO-d_6) δ 6.68 (dd, J=1.7, 3.4 Hz, 1H), 6.94 (s, 1H), 7.25 (dd, J=1, 3.7 Hz, 1H), 7.91 (dd, J=0.8, 1.9 Hz, 1H).

Intermediate A5

Preparation of 6-benzyl-4-chloro-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-amine

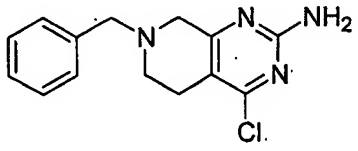


Step 1. Preparation of 2-amino-7-benzyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4(3*H*)-one.



To EtOH (16 mL) cooled to 0 °C (ice/H_2O bath) was added Na spheres (204 mg, 8.9 mmol). The mixture was stirred until all Na dissolved. Methyl 1-benzyl-4-oxo-3-piperidine-carboxylate hydrochloride (3.0 g, 10.1 mmol) and guanidine carbonate (1.4 g, 7.6 mmol) were added. The mixture was refluxed for 16 h. After the reaction was cooled to room temperature, the solid was collected by filtration, washed with EtOH, and dried under vacuum. Desired compound (2.58 g, 10.0 mmol; 99+% yield); mp = 202 - 212 ° (dec.); ES MS $[M+H]^+$= 257; TLC (CH_2Cl_2-MeOH, 90:10); R_f = 0.20.

Step 2. Preparation of 6-benzyl-4-chloro-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-2-amine.

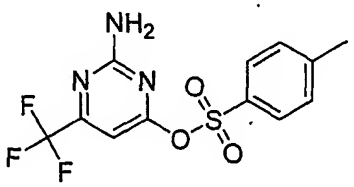


A solution of the product from step 1 (3.5 g, 13.7 mmol) in $POCl_3$ (52 mL) was refluxed under argon for 5 h. The reaction mixture was cooled to room temperature, poured over ice, and allowed to stir at room temperature for 2 h to ensure the quenching of $POCl_3$. At this time, the mixture was made basic upon addition of ammonium hydroxide and was extracted with CH_2Cl_2 (3 x 200 mL). The combined organics were washed with 1N NaOH followed by brine, dried

($MgSO_4$), and concentrated under reduced pressure. The residue was taken up in benzene and was made acidic upon the addition of 1N HCl in diethyl ether. The brown solid was filtered to afford 0.35 g of crude product, which was used without further purification. ES MS $[M+H]^+$=275.

Intermediate A6

Preparation of 2-amino-6-(trifluoromethyl)-4-pyrimidinyl 4-methylbenzenesulfonate

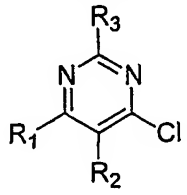


To a solution of 2-amino-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (250 mg, 1.4 mmol), triethylamine (196 μL, 1.4 mmol), *N,N*-dimethylaminopyridine (17 mg, 0.14 mmol), in CH_2Cl_2 (13 mL) cooled to 0 °C was added p-toluenesulfonyl chloride (534 mg, 2.8 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2 , washed with H_2O (2x 20 mL) followed by brine, dried (Na_2SO_4), evaporated, and dried under vacuum. Desired compound (466 mg, 1.4 mmol; 99+% yield; ES MS $[M+H]^+$= 140.

Using the above methods for the preparation of A1-A6 and substituting the appropriate starting materials, the following pyrimidine intermediates were also prepared.

Table 1

Chloropyrimidine Intermediates A

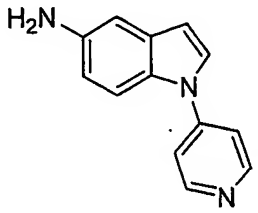


Intermediate No.	R_1	R_2	R_3	Physical Data
A7	Me	H	NH_2	Aldrich
A8	Et	H	NH_2	Aldrich or Lancaster
A9	H	H	NH_2	Aldrich
A10	*t*-Bu	H	NH_2	mp = 109-113 °C; ES MS $[M+H]^+$=186; TLC (90:10 CH_2Cl_2/MeOH); R_f = 0.37.
A11	Me	Cl	NH_2	Aldrich or Lancaster?
A12	-$(CH)_4$-		NH_2	^{1}H NMR (DMSO-d_6) δ 6.60 (s, 2H), 2.55-2.29 (m, 4H), 1.68-1.56 (m, 4H)
A13	-$(CH)_5$-		NH_2	^{1}H NMR (DMSO-d_6) δ 6.65 (s, 2H), 2.72-2.58 (m, 4H), 1.74-1.60 (m, 2H), 1.55-1.34 (m, 4H)
A14	-$(CH)_3$-		NH_2	^{1}H NMR (DMSO-d_6) δ 6.73 (s, 2H), 2.72-2.57 (m, 4H), 1.89 (sept, J = 7.0, 2H)
A15	*i*-Pr	H	NH_2	mp = 104-112 °C; ^{1}H NMR (D_2O) δ 6.11 (s, 1H), 2.23-2.11 (m, 1H), 0.46 (d, J = 6.2 Hz, 6H); ES MS $[M+H]^+$= 172
A16	CH_3	H	Ph-NH-	
A17	Ph	H	NH_2	
A18	3-pyridyl	H	NH_2	
A19	2-pyridyl	H	NH_2	
A20	3-NO_2-Ph	H	NH_2	
A21	Cl	H	NH_2	Aldrich

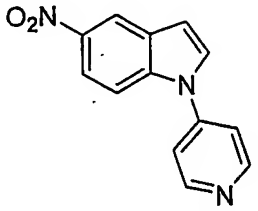
B. Preparation of arylamine intermediates

Intermediate B1

Preparation of 1-(4-pyridinyl)-1*H*-indol-5-amine

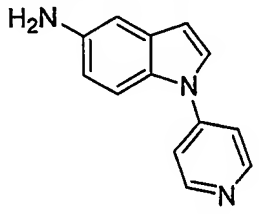


Step 1. Preparation of 5-nitro-1-(4-pyridinyl)-1*H*-indole



To a solution of 5-nitroindole (7.0 g, 43.2 mmol) and 4-chloropyridine hydrochloride (7.8 g, 51.8 mmol) in DMF (43 mL) was added potassium *tert*-butoxide (12.1 g, 108.0 mmol), portionwise. The reaction was heated at 100 °C for 48 h. The mixture was allowed to cool to room temperature and poured into water (400 mL). The resulting solid was removed by filtration and dried under vacuum. Desired compound (6.04 g, 25.3 mmol; 58% yield); ^{1}H NMR (DMSO-d_6) δ 8.76 (dd, J = 1.7, 4.5, 2H), 8.68 (d, J = 2.2, 1H), 8.06-8.13 (m, 2H), 7.92 (d, J = 9.2, 1H), 7.75 (dd, J = 1.5, 4.6, 2H), 7.07 (dd, J = 0.9, 3.5, 1H); ES MS $[M+H]^+$ = 240.

Step 2. Preparation of 1-(4-pyridinyl)-1*H*-indol-5-amine

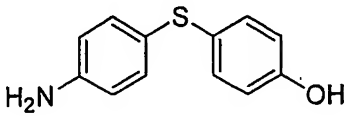


A mixture of the product from step 1 (8.27 g, 34.6 mmol) and 10% palladium-on-charcoal catalyst (827 mg) in ethyl acetate (166 mL) and EtOH (9 mL) was stirred under hydrogen at atmospheric pressure for 48 h. Further catalyst (414 mg) was added and the reaction was stirred for 24 h. Again, further catalyst (414 mg) was added and the reaction was stirred an additional 24 h. The catalyst was removed by filtration through diatomaceous earth and the solvent removed from the filtrate by evaporation. The residue was triturated with ether, collected by filtration, and

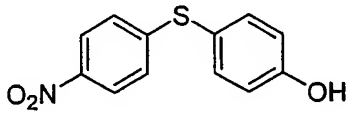
dried under vacuum. Desired compound (4.67 g, 22.3 mmol; 65% yield); mp = 149 - 154 °C; ES MS $[M+H]^+$= 210; TLC (CH_2Cl_2-MeOH, 95:5); R_f= 0.29.

Intermediate B2

Preparation of 4-[(4-aminophenyl)sulfanyl]phenol

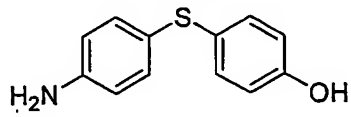


Step 1. Preparation of 4-[(4-nitrophenyl)sulfanyl]phenol.



To a solution of nitrobenzenesulfonyl chloride (4g, 21 mmol) in ether (25 mL) was added phenol (1.97 g, 20 mmol) as a solution in ether (25 mL). After being stirred for 15 h at rt, the mixture was concentrated to afford a crude solid which was recrystallized from acetic acid. Desired compound (4.0 g, 16.2 mmol, 76% yield). TLC (Hexanes/EtOAc, 70:30); R_f= 0.54.

Step 2. Preparation of 4-[(4-aminophenyl)sulfanyl]phenol.

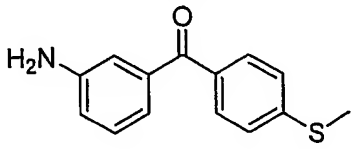


To a solution of the product of step 1 (4g, 16.2 mmol) in EtOH (500 mL) was added $SnCl_2 \cdot 2H_2O$ (18.3 g, 81 mmol) The solution was warmed to reflux. After being stirred for 3 h, the mixture was allowed to cool to rt, and the volatiles were removed by rotary evaporation. The resultant slurry was suspended in EtOAc, and solid $NaHCO_3$ was added. Subsequently, the mixture was filtered, and the filtered solid was washed thoroughly with EtOAc. The organic filtrate was washed with water, and the aqueous washes were extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford an orange solid, which was used without additional purification. Desired compound (3.0 g, 13.8 mmol, 86 % yield).

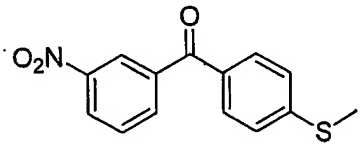
TLC (Hexanes/EtOAc, 70:30); R_f= 0.34.

Intermediate B3

Preparation of (3-aminophenyl)[4-(methylsulfanyl)phenyl]methanone

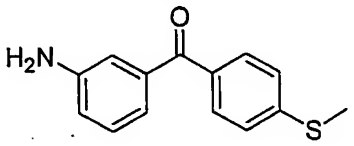


Step 1. Preparation of [4-(methylsulfanyl)phenyl](3-nitrophenyl)methanone



3-nitrobenzoylchloride (5.0 g, 26.94 mmol) was added to a solution of thioanisole (3.16 ml, 26.94 mmol) and 1,2-dichlorethane (95 mL). The resulting reaction mixture was cooled to 0 °C (ice/H_2O bath) and 0.5 equivalents of aluminum trichloride (1.8 g, 13.47 mmol) was added. The reaction was allowed to stir for 15 min at this temperature and the cold bath was removed followed by addition of the remaining equivalents of $AlCl_3$ (2.51 g, 18.87). The reaction solution turned a dark greenish/yellow and was allowed to stir at room temp. for 18h, after which time the reaction was quenched slowly with H_2O (50 mL). The mixture was diluted with CH_2Cl_2 (50 mL) and washed with H_2O (3 x 50 mL), and the combined organic phases were washed with satd $NaHCO_3$ (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (EtOAc/hexane, ¼) to afford 3.3 g (44%) of 4-(methylsulfanyl)phenyl](3-nitrophenyl)methanone as a solid. EI-LRMS *m/z* 274 (M^+); TLC R*f* 0.68 (EtOAc/Hex, 2/3).

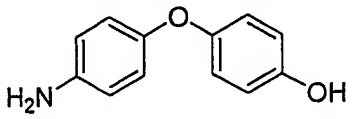
Step 2. Preparation of (3-aminophenyl)[4-(methylsulfanyl)phenyl]methanone



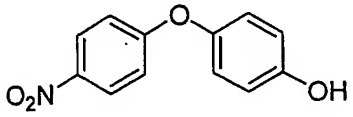
Prepared analogously to Intermediate **B2**, step 2. The crude product was purified by flash column chromatography, eluting with 70:30 Hexanes/EtOAc. TLC: (Hexanes/EtOAc, 70:30); R_f= 0.15.

Intermediate B4

Preparation of 4-(4-aminophenoxy)phenol

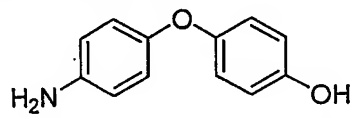


Step 1. Preparation of 4-(4-nitrophenoxy)phenol



A mixture of *p*-nitrofluorobenzene (25 g, 0.177 mol), dihydroquinone (19.5 g, 0.177 mol), and sodium hydroxide (7.08 g, 0.177 mol) in EtOH/H2O (1:1 v/v, 176 mL) was heated at reflux for 20 h, and subsequently allowed to cool to room temperature. The mixture was filtered, the filtrate was made acidic with dilute aqueous HCl, and the resultant precipitate filtered to afford the crude product as a yellow solid. The desired product was recrystallized from EtOH. (15 g, 0.064 mol, 37 % yield). . TLC (Hexanes/EtOAc, 70:30); R_f= 0.44.

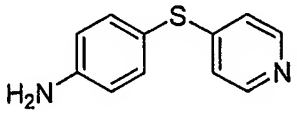
Step 2. Preparation of 4-(4-aminophenoxy)phenol



To a solution of the product of step 1 in EtOH (100 mL) was added 10% palladium on carbon (200 mg). After being stirred under an atmosphere of hydrogen overnight, the mixture was filtered through Celite®. The volatiles were removed from the filtrate to provide the crude product which was purified by flash column chromatography eluting with Hexanes/EtOAc (85:15, followed by 75:25). Desired product (1.5 g, 7.45 mmol; 86 %). TLC (Hexanes/EtOAc, 70:30); R_f= 0.41.

Intermediate B5

Preparation of 4-(4-pyridinylthio)aniline

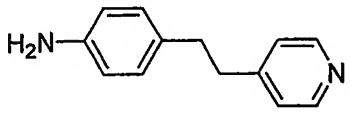


To a solution of 4-aminothiophenol (20.2 g, 156.5 mmol) in anhydrous DMF (200 mL) was added 4-chloropyridine hydrochloride (24.4 g, 161.0 mmol) followed by potassium

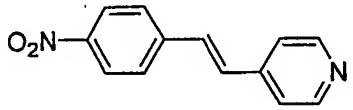
carbonate (44 g, 318.4 mmol). The reaction mixture was heated at 80 °C overnight, then diluted with ethyl acetate (400 mL) and water (400 mL). The aqueous layer was back-extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with a saturated aqueous NaCl solution (200 mL), dried over anhy $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a pad of silica with ethyl acetate and the resulting material was triturated with an ethyl ether / hexane solution to afford the desired product (24.7 g, 78%). TLC (50% ethyl acetate / 50% hexane) R_f 0.25; ^{1}H-NMR (DMSO-d_6) δ 5.67 (bs, 2H), 6.65 (d, J=8.4 Hz, 2H), 6.88 (d, J=6.2 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 8.27 (d, J=6.2 Hz, 2H), MS[M+H]$^+$ = 203.

Intermediate B6

Preparation of 4-[2-(4-pyridinyl)ethyl]aniline



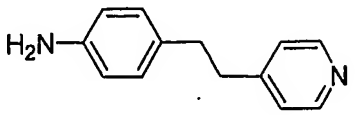
Step1. Preparation of 4-[(*E*)-2-(4-nitrophenyl)ethenyl]pyridine



To an oven dried 500 mL 3-necked flask was added (4-nitrobenzyl)triphenylphosphonium bromide (15 g, 30.42 mmol) followed by the addition of THF (100 mL). The solution was cooled to 0 °C in an ice bath. Potassium *t*-butoxide (3.9 g, 33.02 mmol) was then added in one portion resulting in an orange suspension. The suspension was maintained at 0 °C while a solution of 4-pyridine-2-carboxaldehyde (2.7 g, 24.70 mmol) in THF (20 mL) was added in 10 minutes. The ice bath was removed and the reaction was stirred at room temperature for 2 h. At this time, the reaction was quenched with saturated ammonium chloride solution (50 mL) and stirred for 15 minutes. The mixture was then extracted with ethyl acetate (2 x 100 mL), the combined extracts was washed with saturated aqueous NaCl solution (100 mL) and dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue was chromatographed on silica with 0-50% ethyl acetate in hexanes to afford the desired product (1.8 g, 32%). TLC (50% ethyl acetate / 50% hexane) R_f 0.28; ^{1}H-

NMR (DMSO-d_6) δ 6.84 (d, J=12.4Hz, 1H), 6.96 (d, J=12.4Hz, 1H), 7.14 (d, J=6.2Hz, 2H), 7.45 (d, J=8.7Hz, 2H), 8.15 (d, J=8.7Hz, 2H), 8.47 (d, J=6.2Hz, 2H).

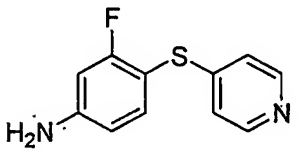
Step 2. Preparation of 4-[2-(4-pyridinyl)ethyl]aniline



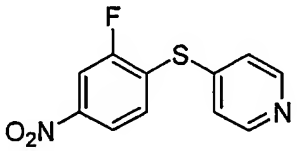
To a dry 50 mL flask flushed with argon was added 10% Pd on carbon (285 mg) followed by the addition of ethanol (12 mL) and the product from step 1 (1.8 g, 8.0 mmol). At this time, the argon line was replaced with a hydrogen balloon and the reaction was stirred overnight. The mixture was filtered through a pad of Celite® and the filtrate was concentrated at reduced pressure. The solid residue was triturated with ethyl ether/hexanes to afford the desired product (1.2 g, 67%). TLC (4% acetone / 96% methylene chloride) R_f 0.09; ^{1}H-NMR (DMSO-d_6) δ 2.67-2.83 (m, 4H), 4.83 (bs, 2H), 6.45 (d, J=8.2Hz, 2H), 6.84 (d, J=8.2Hz, 2H), 7.20 (d, J=6Hz, 2H), 8.41 (d, J=6Hz, 2H).

Intermediate B7

Preparation of 3-fluoro-4-(4-pyridinylsulfanyl)aniline



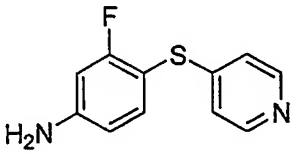
Step 1. Preparation of 4-[(2-fluoro-4-nitrophenyl)sulfanyl]pyridine.



A solution of 4-mercaptopyridine (4.2 g, 35.6 mmol), 3,4-difluoronitrobenzene (5.7 g, 35.7 mmol), and potassium carbonate (12.4 g, 89.7 mmol) in anhydrous DMF (40 mL) was stirred at 40 °C and under argon for 3 h. TLC showed complete reaction. The mixture was diluted with ethyl acetate (100 mL) and water (100 mL) and the aqueous layer was back-extracted with ethylacetate (2 x 100 mL). The organic layers were washed with a saturated NaCl solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography with 50% ethyl acetate / 50% hexanes. It afforded the desired product as a yellow solid (6.3 g, 71%). TLC (50% EtOAc/50% hexane) R_f 0.53; ^{1}H-

NMR (DMSO-d_6) δ 7.27 (dd, J=0.76, 4.2 Hz, 2H), 7.78 (dt, J=0.76, 7.2 Hz, 1H), 8.11-8.15 (m, 1H), 8.28-8.33 (m, 1H), 8.5 (dd, J= 1.4, 4.6 Hz, 2H), MS $[M+H]^+$= 251.

Step2. Preparation of 3-fluoro-4-(4-pyridinylsulfanyl)aniline.

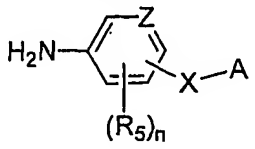


A slurry of 3-fluoro-4-pyridinylthio)nitrobenzene (6.3 g, 25.2 mmol), iron powder (6.0 g, 107.4 mmol), acetic acid (100 mL), and water (1 mL) were stirred at room temperature overnight. The mixture was diluted with Et_2O (100 mL) and water (100 mL). The aqueous phase was adjusted to pH 5 with a 4 N NaOH solution. The combined organic layers were washed with an aqueous saturated NaCl solution (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography with 50% ethyl acetate / 50% hexanes. It afforded the desired product as a white solid (4.8 g, 86%). TLC (50% EtOAc/50% hexane) R_f 0.28; ^{1}H-NMR (DMSO-d_6) δ 6.04 (bs, 2H), 6.47-6.51 (m, 2H), 6.91 (d, J=6.1 Hz, 2H), 7.22 (t, J=8.4 Hz, 1H), 8.30 (d, J=6.4 Hz, 2H).

Using similar methods to those described for the preparation of Intermediates B1-B7, the following additional compounds were also prepared:

Table 2

Arylamine Intermediates B



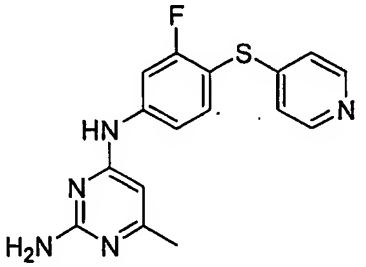
Intermediate No.	Z	$(R_5)_n$	-X-	A	Physical Properties
B8	CH	H	(4)-S-CH_2-	pyrid-4-yl	TLC Rf = 0.12 (50% EtOAc/50% hexanes). 1H NMR (DMSO-*d6*) δ 3.91 (s, 2H), 5.26 (bs, 2H), 6.44 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 6.3 Hz, 2H), 8.40 (d, J = 6.0 Hz, 2H).
B9	CH	3-CF_3	(4)-S-	pyrid-4-yl	TLC Rf = 0.10 (50% EtOAc/50% hexanes). 1H NMR (DMSO-*d6*) δ 6.21 (bs, 2H), 6.84-6.87 (m, 3H), 7.10 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 6.3 Hz, 2H).
B10	CH	H	(4)-O-	isoquinolin-5-yl	
B11	CH	3-F	(4)-O-	isoquinolin-5-yl	1H NMR (DMSO-*d6*) δ 5.42 (bs, 2H), 6.41-6.55 (m, 2H), 6.81-7.05 (m, 2H), 7.48-7.54 (m, 1H), 7.73-7.76 (m, 1H), 8.06-8.08 (m, 1H), 8.54-8.56 (m, 1H), 9.32 (s, 1H).
B12	CH	3,5-$(Cl)_2$	(4)-O-	isoquinolin-5-yl	TLC Rf = 0.29 (45% EtOAc/55% hexanes). 1H NMR (DMSO-*d6*) δ 5.73 (bs, 2H), 6.69 (dd, J = 1.1 and 8.0 Hz, 1H), 6.75 (s, 2H), 7.51 (t, J = 7.7 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 5.9 Hz, 1H), 8.58 (d, J = 5.6 Hz, 1H), 9.34 (bs, 1H).
B13	CH	H	(4)-S-	pyrid-4-yl	TLC Rf = 0.07 (100% EtOAc). 1H NMR (DMSO-*d6*) δ 5.84 (bs, 2H), 6.95-6.99 (m,

Intermediate No.	Z	$(R_5)_n$	-X-	A	Physical Properties
					3H), 7.32 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 2.8 Hz, 1H), 8.31 (d, J = 4.7 Hz, 2H).
B14	CH	3,5-$(Cl)_2$	(4)-S-	pyrid-4-yl	1H NMR (DMSO-*d6*) δ 6.30 (bs, 2H), 6.82 (s, 2H), 6.89, (d, J = 6.0 Hz, 2H), 8.33 (d, J = 6.1 Hz, 2H).
B15	CH	2,5-$(F)_2$	(4)-S-	pyrid-4-yl	
B16	CH	3-Cl	(4)-S-	pyrid-4-yl	
B17	CH	H	(4)-S-	isoquinolin-5-yl	
B18	CH	H	(4)-CH_2-S-	pyrid-4-yl	
B19	CH	H	(4)-S-	pyrid-3-yl	
B20	CH	H	(3)-S-	pyrid-4-yl	
B21	CH	H	(4)-O-	quinolin-5-yl	

C. Preparation of Examples of the Invention

Example 1

Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[3-fluoro-4-(4-pyridinylsulfanyl)phenyl]amine

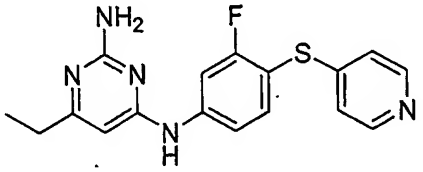


A suspension of 2-amino-4-chloro-6-methylpyrimidine (Intermediate A7, 0.2 g, 1.3 mmol), 3-fluoro-4-(4-pyridinylthio)aniline (Intermediate B7, 0.3 g, 1.3 mmol), and K_2CO_3 (0.2 g, 1.3 mmol) in *o*-xylene (1.3 mL) was heated to 100 °C in a 5 mL reaction-vial overnight. The reaction mixture was diluted with MeOH and coated on silica and purified by MPLC (Biotage) with 5-7% MeOH in CH_2Cl_2. It afforded 74 mg of product (18% yield). TLC (6% MeOH/94% CH_2Cl_2) R_f 0.29; MS ES 328 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.12 (s, 3H), 5.92 (s, 1H), 6.38

(bs, 2H), 6.96 (d, *J*=5.1 Hz, 2H), 7.39-7.52 (m, 2H), 8.26 (d, *J*=11.9 Hz, 1H), 8.33 (d, *J*=4.8 Hz, 2H), 9.55 (bs, 1H).

Example 2

Preparation of 6-ethyl-*N*4-[3-fluoro-4-(4-pyridinylsulfanyl)phenyl]-2,4-pyrimidinediamine

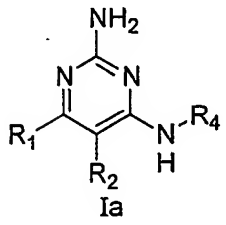


2-Amino-4-chloro-6-ethylpyrimidine (Intermediate A8, 55.1 mg, 0.25 mmol) and Intermediate B7(39.4 mg, 0.25 mmol) were suspended in 0.01 M aqueous HCl (500 μL). The mixture was refluxed for 6 h. The reaction was cooled to room temperature and the solvent was evaporated by vacuum. The residue was purified by reversed phase chromatography on a YMC Pack-pro C18 column (trademark) eluting with acetonitrile/H_2O (10:90 – 90:10 gradient). The compound was further purified by preparative TLC eluting with CH_2Cl_2-MeOH (90:10). Desired compound (2.9 mg, 0.0085 mmol; 34% yield); ^{1}H NMR (Methanol-d_4) 8.16 (dd, J = 1.7, 4.7, 2H), 8.00 – 8.04 (m, 1H), 7.37 (m, 2H), 6.93 (dd, J = 1.8, 4.9, 2H), 5.91 (s, 1H), 2.39 (q, J = 7.7, 2H), 1.13 (t, J = 7.5, 3H); ES MS $[M+H]^+$ = 342 ; TLC (CH_2Cl_2-MeOH, 90:10); R_f = 0.48.

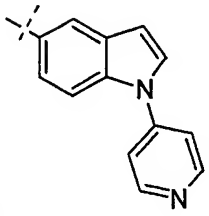
Examples 3-26

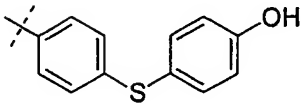
Using the above procedures, the following examples of pyridines were synthesized and are summarized in Table 3.

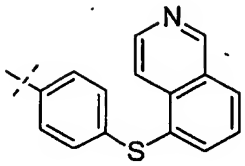
Table 3

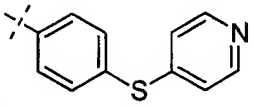


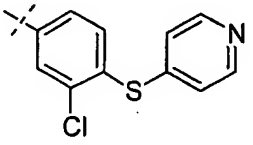
Ia

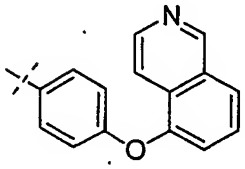
a. 

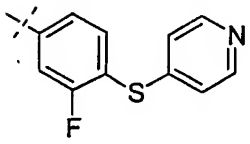
d. 

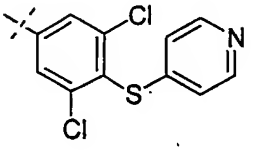
g. 

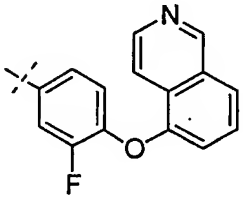
b. 

e. 

h. 

c. 

f. 

i. 

Ex. No.	Intermediate Pyrimidone (A)	Intermediate Amine (B)	R_1	R_2	R_4	Analytical Data
3	A9	B1	H	H	a	mp = 245 – 247 °C; ^{1}H NMR (Methanol-d_4) 8.79 (d, J = 5.7, 2H), 8.32 (s, 1H), 8.13 (d, J = 5.9, 2H), 7.97 (d, J=9.2, 1H), 7.88 (d, J = 3.6, 1H), 7.71 (d, J = 7.3, 1H), 7.56 (d, J = 9.1, 1H), 6.94 (d, J = 4.0, 1H), 6.33 (d, J = 7.6, 1H); ES MS $[M+H]^+$ = 303.
4	A1	B1	CH_3CH_2-	H	a	mp = 230 – 233 °C; ^{1}H NMR (DMSO-d_6) 12.43 (s, 1H), 10.51 (s, 1H), 8.79 (d, J = 6.3, 2H), 8.22 (s, 1H), 7.87 – 8.23 (m, 5H), 7.46 (d, J = 8.4, 1H), 6.85 (d, J = 3.3, 1H), 6.14 (s, 1H), 2.51 – 2.61 (m, 2H), 1.19 (t, J = 7.5, 3H); ES MS $[M+H]^+$ = 331.
5	A1	B1	CH_3-	Cl	a	mp = 238 – 241 °C; ES MS $[M+H]^+$ = 351; TLC: R_f = 0.71 (CH_2Cl_2-MeOH, 95:5).
6	A1	B1	-$(CH_2)_4$-		a	^{1}H NMR (DMSO-d_6) 11.75 (s, 1H), 10.59 (s, 1H), 8.78 (d, J = 5.4, 2H), 8.21 (s, 1H), 7.87 – 7.97 (m, 5H), 7.47 (d, J = 8.1, 1H), 6.85 (d, J = 3.4, 1H), 6.21 (s, 1H), 1.29 (s, 9H); ES MS $[M+H]^+$ = 359.
7	A1	B1	-$(CH_2)_3$-		a	^{1}H NMR (Methanol-d_4) 8.80 (d, J = 6.4, 1H), 8.21 (d, J = 6.6, 1H), 8.16 (s, 1H), 7.99 (d, J = 8.9, 1H), 7.90 (d, J = 3.3, 1H), 7.60 (d, J = 8.9, 1H), 6.96 (d, J = 4.0, 1H), 2.93 – 2.99 (m, 2H), 2.86 (s, 2H), 2.23 – 2.29 (m, 2H); ES MS $[M+H]^+$ = 343; TLC: R_f = 0.46 (CH_2Cl_2-MeOH, 90:10.

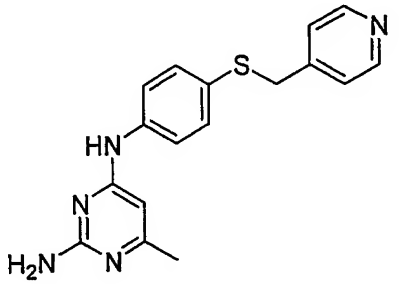
Ex. No.	Intermediate Pyrimidone (A)	Intermediate Amine (B)	R_1	R_2	R_4	Analytical Data
8	Aldrich	B1	H	H	b	^{1}H NMR (Methanol-d_4) 8.13 (dd, J = 1.4, 4.6, 2H), 7.80 (dd, J = 2.0, 6.7, 2H), 7.71 (d, J = 6.4, 1H), 7.38 – 7.42 (m, 2H), 6.92 (dd, J = 1.6, 4.7, 2H), 6.01 (d, J = 6.1, 1H); ES MS $[M+H]^+$ = 296; TLC: R_f = 0.28 (CH_2Cl_2-MeOH, 90:10);.
9	A1	B1	$(CH_3)_3C$-	H	b	mp = 126 – 129 °C; ES MS $[M+H]^+$ = 352; TLC: R_f = 0.62 (CH_2Cl_2-MeOH, 90:10..
10	A1	B1	CH_3-	Cl	b	^{1}H NMR (Methanol-d_4) 8.43 (d, J = 5.9, 2H), 7.93 – 7.96 (m, 2H), 7.68 – 7.71 (m, 2H), 7.46 (d, J = 6.6, 2H), 2.51 (s, 3H); ES MS $[M+H]^+$ = 344.
11	A1	B1	-$(CH_2)_4$-		b	mp = 321 – 324 °C; ^{1}H NMR (DMSO-d_6) 9.35 (s, 1H), 8.37 (dd, J = 1.4, 4.7, 2H), 7.91 (d, J = 8.9, 2H), 7.58 (d, J = 8.4, 2H), 7.02. (dd, J = 1.5, 4.6, 2H), 3.33 (br s, 4H), 2.60 (br s, 2H), 1.77 (br s, 4H); ES MS $[M+H]^+$ = 350.
12	Aldrich	B1	H	H	c	^{1}H NMR (Methanol-d_4) 8.26 (dd, J = 1.4, 4.7, 2H), 8.11 – 8.16 m, 1H), 7.84 (d, J = 6.2, 1H), 7.45 – 7.50 (m, 2H), 7.04 (dd, J = 1.6, 4.9, 2H), 6.11 (d, J = 6.1, 1H); ES MS $[M+H]^+$ = 314; TLC: R_f = 0.40 (CH_2Cl_2-MeOH, 90:10).
13	A1	B1	$(CH_3)_3C$-	H	c	^{1}H NMR (Methanol-d_4) 8.25 – 8.27 (m, 2H), 8.11 – 8.16 (m, 1H), 7.46 – 7.48 (m, 2H), 7.03 (d, J = 4.9, 2H), 6.15 (s, 1H), 1.28 (s, 9H); ES MS $[M+H]^+$ = 370; TLC: R_f = 0.55 (CH_2Cl_2-MeOH, 90:10).
14	A1	B1	-$(CH_2)_4$-		c	mp = 248 – 250 °C, ES MS $[M+H]^+$ = 368; TLC: R_f = 0.56 (CH_2Cl_2-MeOH, 90:10).

Ex. No.	Intermediate Pyrimidone (A)	Intermediate Amine (B)	R_1	R_2	R_4	Analytical Data
15	A1	B1	$-(CH_2)_5-$		c	^{1}H NMR (Methanol-d_4) 8.78 (d, J = 6.6, 2H), 8.52 (d, J = 5.9, 1H), 8.34 (br s, 1H), 7.76 (d, J = 6.9, 2H), 7.42 (d, J = 6.1, 1H), 7.23 – 7.33 (m, 1H), 7.11 (br s, 1H), 6.51 – 6.58 (m, 3H), 2.85 – 2.87 (m, 2H), 2.60 – 2.63 (m, 1H), 2.31 – 2.34 (m, 2H), 1.42 – 1.75 (m, 6H); ES MS $[M+H]^+$ = 382.
16	A1	B1	CH_3-	H	d	mp = 254-256 °C, TLC: R_f = 0.03 (95:5 CH_2Cl_2/MeOH).
17	A7	B16	CH_3-	H	e	TLC: R_f = 0.23 (6% MeOH/94% CH_2Cl_2); LC MS $[M+H]^+$ 344; (3.37 min)
18	A7	B10	CH_3-	H	h	TLC: R_f = 0.39 (6% MeOH/94% CH_2Cl_2) LC MS $[M+H]^+$ 345; (3.07 min)
19	A7	B17	CH_3	H	g	TLC: R_f = 0.44 (6% MeOH/94% CH_2Cl_2) LC'MS $[M+H]^+$ 360; (2.64 min)
20	A17	B7	Ph	H	c	TLC: R_f = 0.26 (4% MeOH/96% CH_2Cl_2); LCMS: ES $[M+H]^+$ 390; (2.76 min)
21	A18	B14	3-pyridyl	H	f	TLC: R_f = 0.37 (6% MeOH/94% CH_2Cl_2); LCMS: ES m/z 441 (1.65 min)
22	A18	B5	3-pyridyl	H	b	TLC: R_f = 0.35 (4% MeOH/96% CH_2Cl_2); LCMS: ES $[M+H]^+$373; (2.61 min)
23	A2	B5	4-pyridyl	H	b	TLC: R_f=0.13 (4% MeOH/96% CH_2Cl_2) LCMS: ES $[M+H]^+$ 373; (2.56 min)
24	A17	B11	Ph	H	i	TLC: R_f = 0.21 (2% MeOH/98% CH_2Cl_2); LCMS: ES $[M+H]^+$ 424; (2.75 min)
25	A2	B11	4-pyridyl	H	i	TLC: R_f=0.35 (6% MeOH/94% CH_2Cl_2); LCMS: ES $[M+H]^+$ 425; (2.60 min)
26	A7	B5	CH_3	H	b	LCMS: ES $[M+H]^+$ 310; (3.53 min)

By selecting combinations of the appropriate Intermediates A1-A21 with Intermediates B1-B17, a variety of products were prepared in like manner and are described in Example 27-31.

Example 27

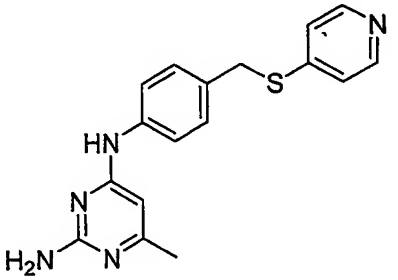
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-{4-[(4-pyridinylmethyl)sulfanyl]phenyl}amine



Prepared in 34% yield from Intermediate A7 and B8: TLC (7% MeOH in CH_2Cl_2) R_f 0.36; MS (ES) 324 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.09 (s, 3H), 4.12 (s, 2H), 5.87 (s, 1H), 6.33 (bs, 2H), 7.19 (d, *J*=8.5 Hz, 2H), 7.23 (d, *J*=5.8 Hz, 2H), 7.64 (d, *J*=8.5 Hz, 2H), 8.43 (d, *J*=5.3 Hz, 2H), 9.20 (bs, 1H).

Example 28

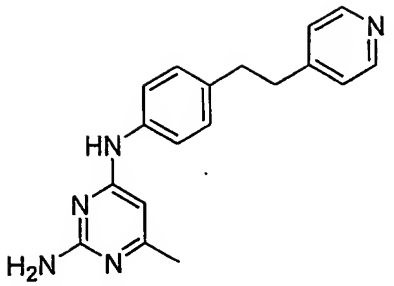
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-{4-[(4-pyridinylsulfanyl)methyl]phenyl}amine



Prepared in 6% yield from Intermediate A7 and B18:TLC (7% MeOH in CH_2Cl_2) R_f 0.38; MS (ES) 342 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) 8 2.06 (s, 3H), 4.30 (s, 2H), 5.84 (s, 1H), 6.13 (bs, 2H), 7.27-7.31 (m, 4H), 7.63 (d, *J*=7.9 Hz, 2H), 8.33 (d, *J*=6.1Hz, 2H), 8.99 (bs, 1H).

Example 29

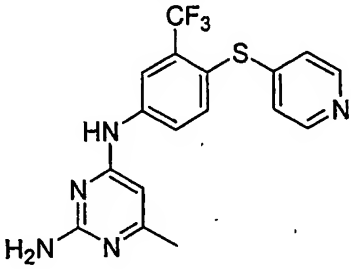
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-{4-[2-(4-pyridinyl)ethyl]phenyl}amine



Prepared in 30% yield from A7 and B6: TLC (8% MeOH in CH_2Cl_2) R_f 0.34; MS (ES) 306 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.06 (s, 3H), 2.83-2.87 (m, 4H), 5.82 (s, 1H), 6.09 (bs, 2H), 7.07 (d, *J*=8.5 Hz, 2H), 7.21 (d, *J*=5.8 Hz, 2H), 7.54 (d, *J*=8.5 Hz, 2H), 8.41 (d, *J*=6.2 Hz, 2H), 8.87 (s, 1H).

Example 30

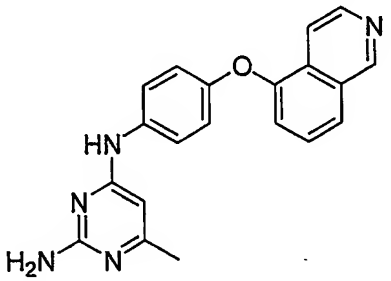
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[4-(4-pyridinylsulfanyl)-3-(trifluoromethyl)phenyl]amine



Prepared in 1.2% yield from A7 and B9: TLC (7% MeOH in CH_2Cl_2) R_f 0.39; MS (ES) 378 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.03 (s, 3H), 5.94 (s, 1H), 6.33 (bs, 2H), 6.91 (d, *J*=6.5 Hz, 2H), 7.64 (d, *J*=8.9 Hz, 1H), 8.19 (d, *J*=2.2 Hz, 1H), 8.33 (d, *J*=5.9 Hz, 2H), 8.37 (dd, *J*=2.1, 8.6 Hz, 1H), 9.66 (s, 1H).

Example 31

Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[4-(5-isoquinolinyloxy)phenyl]amine

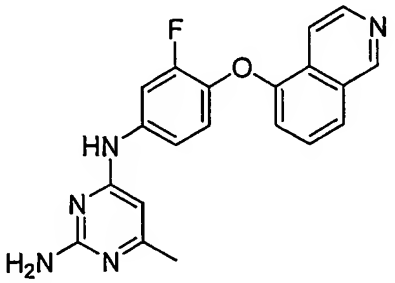


Prepared in 30% yield from A7 and B10: TLC (6% MeOH in CH_2Cl_2) R_f 0.39; MS (ES) 344 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.08 (s, 3H), 5.85 (s, 1H), 6.11 (bs, 2H), 7.02-7.08 (m, 3H),

7.58 (t, *J*=8.1 Hz, 1H), 7.74 (d, *J*=8.6 Hz, 2H), 7.84 (d, *J*=8.2 Hz, 1H), 7.98 (d, *J*=5.8 Hz, 1H), 8.54 (d, *J*=5.9 Hz, 1H), 9.03 (bs, 1H), 9.35 (bs, 1H).

Example 32

Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[3-fluoro-4-(5-isoquinolinyloxy)phenyl]amine

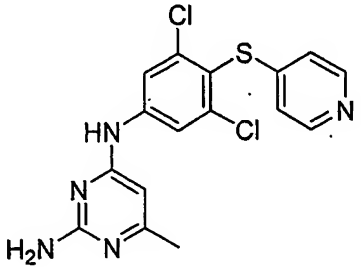


A suspension of 2-amino4-chloro-6-methylpyrimidine (Intermediate A7, 0.14 g, 1.0 mmol), 3-fluoro-4-(5-isoquinolin-oxy)aniline (Intermediate B10, 0.25 g, 1.0 mmol), and HCl (0.1 mL) in H_2O (1.0 mL) was heated to 70 °C in a 5 mL reaction vial overnight. The reaction mixture was diluted with MeOH, treated with saturated $NaHCO_3$, and coated on silica and purified by MPLC (Biotage) with 5% MeOH in CH_2Cl_2. It afforded 52 mg of product (14% yield). TLC (6% MeOH/94% CH_2Cl_2) R_f 0.45; MS (ES) 362 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.10 (s, 3H), 5.88 (s, 1H), 6.29 (bs, 2H), 6.93 (d, *J*=7.9 Hz, 1H), 7.22 (t, *J*=8.9 Hz, 1H), 7.34 (dd, *J*=1.7, 8.9 Hz, 1H), 7.55 (t, *J*=8.1 Hz, 1H), 7.82 (d, *J*=8.3 Hz, 1H), 8.08 (d, *J*=5.6 Hz, 1H), 8.21 (dd, *J*=2.6, 14.2 Hz, 1H), 8.58 (d, *J*=5.9 Hz, 1H), 9.30 (bs, 1H), 9.36 (s, 1H).

Using the above-described method for Example **32**, Examples **33-41** were similarly prepared.

Example 33

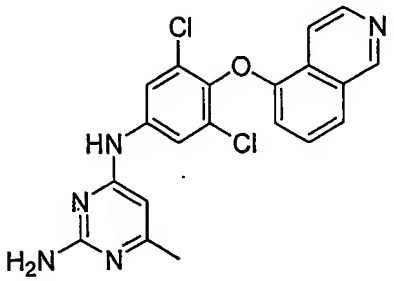
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[3,5-dichloro-4-(4-pyridinylsulfanyl)phenyl]amine



Prepared in 10% yield from A7 and B14: TLC (5% MeOH in CH_2Cl_2) R_f 0.14; MS (ES) 378 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.14 (s, 3H), 5.92 (s, 1H), 6.49 (bs, 2H), 6.93 (d, *J*=6.1 Hz, 2H), 8.13 (s, 2H), 8.35 (d, *J*=6.2 Hz, 2H), 9.63 (bs, 1H).

Example 34

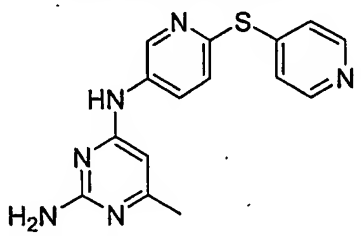
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[3,5-dichloro-4-(5-isoquinolinyloxy)phenyl]amine



Prepared in 58% yield from A7 and B12: TLC (70% EtOAc/30% hexanes) R_f 0.18; MS (ES) 412 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.13 (s, 3H), 5.89 (s, 1H), 6.38 (bs, 2H), 6.73 (d, *J*=7.6 Hz, 1H), 7.52 (t, *J*=7.9 Hz, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 8.05 (s, 2H), 8.16 (d, *J*=5.8 Hz, 1H), 8.61 (d, *J*=5.9 Hz, 1H), 9.36 (s, 1H), 9.42 (s, 1H).

Example 35

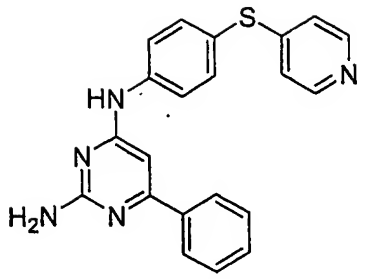
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[6-(4-pyridinylsulfanyl)-3-pyridinyl]amine



Prepared in 16% yield from A7 and B13: TLC (6% MeOH in CH_2Cl_2) R_f 0.16; MS (ES) 311 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 2.11 (s, 3H), 5.91 (s, 1H), 6.34 (bs, 2H), 7.15 (d, *J*=6.2 Hz, 2H), 7.48 (d, *J*=8.8 Hz, 1H), 8.30 (dd, *J*=2.5, 8.4 Hz, 1H), 8.38 (d, *J*=6.1 Hz, 2H), 9.00 (d, *J*=2.4 Hz, 1 H), 9.45 (bs, 1H).

Example 36

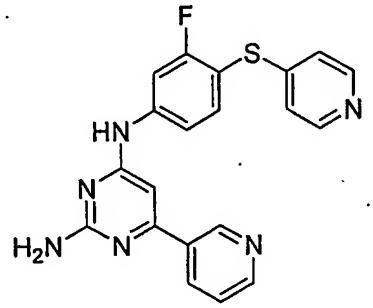
Preparation of *N*-(2-amino-6-phenyl-4-pyrimidinyl)-*N*-[4-(4-pyridinylsulfanyl)phenyl]amine



Prepared in 65% yield from A17. TLC (4% MeOH in CH_2Cl_2) R_f 0.22; MS (ES) 372 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 6.46 (bs, 2H), 6.55 (s, 1H), 6.96 (d, J=4.8 Hz, 2H), 7.46-7.49 (m, 5H), 7.91-8.00 (m, 4H), 8.32 (d, J=4.9 Hz, 2H), 9.57 (bs, 1H).

Example 37

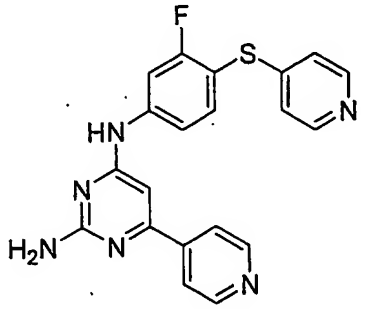
Preparation of *N*-[2-amino-6-(3-pyridinyl)-4-pyrimidinyl]-*N*-[3-fluoro-4-(4-pyridinylsulfanyl)phenyl]amine



Prepared in 45% yield. TLC (4% MeOH in CH_2Cl_2) R_f 0.27; MS (ES) 391 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 6.58 (s, 1H), 6.70 (bs, 2H), 6.99 (d, J=6.4 Hz, 2H), 7.46-7.57 (m, 3H), 8.23-8.36 (m, 4H), 8.65 (d, J=4.4 Hz, 1H), 9.09 (s, 1H), 9.86 (bs, 1H).

Example 38

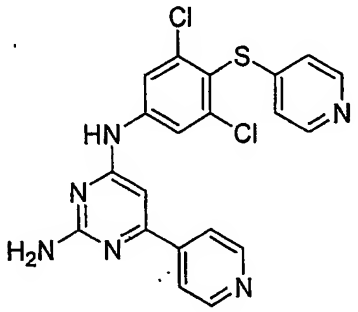
Preparation of *N*-[2-amino-6-(4-pyridinyl)-4-pyrimidinyl]-*N*-[3-fluoro-4-(4-pyridinylsulfanyl)phenyl]amine



Prepared in 22% yield from A2 and B7:. TLC (6% MeOH in CH_2Cl_2) R_f 0.32; MS (ES) 391 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 6.63 (s, 1H), 6.74 (bs, 2H), 6.99 (d, *J*=5.8 Hz, 2H), 7.46-7.58 (m, 2H), 7.85 (d, *J*=5.8 Hz, 2H), 8.31-8.36 (m, 3H), 6.70 (d, *J*=4.3 Hz, 2H), 9.92 (bs, 1H).

Example 39

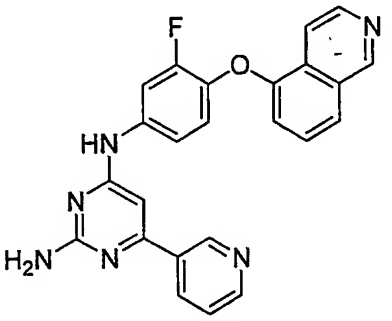
Preparation of *N*-[2-amino-6-(4-pyridinyl)-4-pyrimidinyl]-*N*-[3,5-dichloro-4-(4-pyridinylsulfanyl)phenyl]amine



Prepared in 0.4% yield from A2 and B14: TLC (4% MeOH in CH_2Cl_2) R_f 0.15; ^{1}H-NMR (DMSO-d_6) δ 6.60 (s, 1H), 6.82 (bs, 2H), 6.95 (d, *J*=5.9 Hz, 2H), 7.85 (d, J=5.9 Hz, 2H), 8.18 (s, 2H), 8.36 (d, *J*=3.8 Hz, 2H), 8.71 (d, *J*=4.7 Hz, 2H), 9.99 (bs, 1H).

Example 40

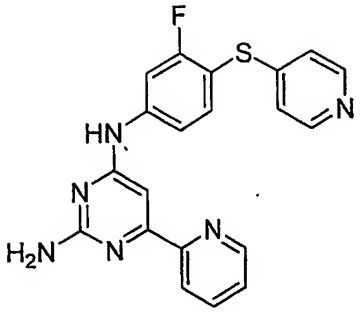
Preparation of *N*-[2-amino-6-(3-pyridinyl)-4-pyrimidinyl]-*N*-[3-fluoro-4-(5-isoquinolinyloxy)phenyl]amine



Prepared in 54% yield from A18 and B11: TLC (5% MeOH in CH_2Cl_2) R_f 0.34; MS (ES) 425 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 6.53 (s, 1H), 6.59 (bs, 2H), 6.96 (d, *J*=7.4 Hz, 1H), 7.26 (t, *J*=9.6 Hz, 1H), 7.38-7.59 (m, 3H), 7.83 (d, *J*=8.2 Hz, 1H), 8.09 (d, *J*=5.7 Hz, 1H), 8.23-8.31 (m, 2H), 8.58-8.65 (m, 2H), 9.09 (bs, 1H), 9.37 (bs, 1H), 9.61 (bs, 1H).

Example 41

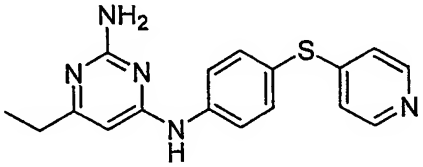
Preparation of *N*-[2-amino-6-(2-pyridinyl)-4-pyrimidinyl]-*N*-[3-fluoro-4-(4-pyridinylsulfanyl)phenyl]amine



Prepared in 60% yield from A19 and B7: TLC (50% EtOAc/50% hexanes) R_f 0.14; MS (ES) 391 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6) δ 6.63 (bs, 2H), 6.98 (d, J=6.6 Hz, 2H), 7.17 (s, 1H), 7.45-7.57 (m, 3H), 7.93 (dt, J=1.9, 7.7 Hz, 1H), 8.23-8.37 (m, 4H), 8.65-8.67 (m, 1H), 9.90 (bs, 1H).

Example 42

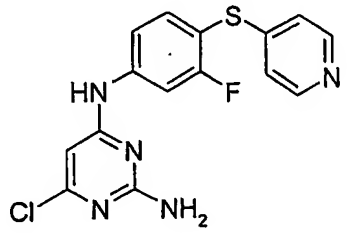
Preparation of *N*-(2-amino-6-ethyl-4-pyrimidinyl)-*N*-[4-(4-pyridinylsulfanyl)phenyl]amine



A mixture of Intermediate B5(50.6 mg, 0.250 mmol) and 2-amino - 4- ethyl-6-chloropyrimidine (Intermediate A8, 39.4 mg, 0.25 mmol) in 0.01 M aqueous HCl (500 μL) was refluxed for 6 h. The reaction was cooled to room temperature and the solvent was evaporated by vacuum. The residue was purified by reverse phase chromatography on a YMC Pack-pro® C18 column eluting with acetonitrile/H_2O (10:90 – 90:10 gradient) to give the desired compound (13.0 mg, 0.040 mmol; 16% yield); mp = 181 - 186 °C; ES MS $[M+H]^+$= 324; TLC (CH_2Cl_2 – MeOH, 95:5); R_f = 0.41.

Example 43

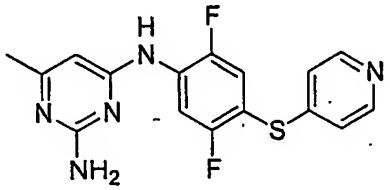
Preparation of of *N*-(2-amino-6-chloro-4-pyrimidinyl)-*N*-[3-fluoro-4-(4-pyridinylsulfanyl)phenyl]amine



2-Amino-4,6 dichloropyrimidine (A21, 12 mmol) and 3-fluoro-4-(4-pyridinylthio)-aniline (B7,12 mmol) were suspended in water (150 mL) and treated with 10 drops of concentrated hydrochloric acid. The mixture was stirred at 100 °C overnight. The clear solution was then neutralized with ammonium hydroxide. The precipitated yellow product was filtered, washed with water, and purified by column chromatography with 1-3% MeOH in CH_2Cl_2 to give the desired product as a white solid (1.98 g, 47%).

Example 44

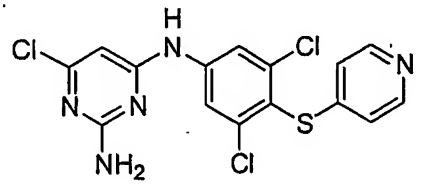
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[2,5-difluoro-4-(4-pyridinylsulfanyl)phenyl]amine



The compound was prepared using a similar method used for the preparation of Example 1 (described above) from A7 and B15: HPLC/MS: $[M+H]^+$ 346.1 *m/z*. Retention time (HPLC/MS) = 1.39 min.

Example 45

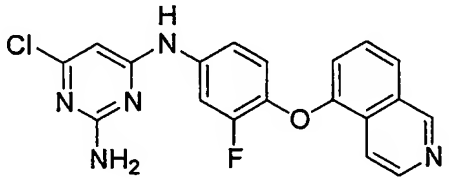
Preparation of *N*-(2-amino-6-chloro-4-pyrimidinyl)-*N*-[3,5-dichloro-4-(4-pyridinylsulfanyl)phenyl] amine



The compound was prepared using a similar method used for the preparation of Example 43 (described above) from A21 and B14: HPLC/MS: $[M+H]^+$ 399.0 *m/z*. Retention time (HPLC/MS) = 3.02 min.

Example 46

Preparation of *N*-(2-amino-6-chloro-4-pyrimidinyl)-*N*-[3-fluoro-4-(5-isoquinolinyloxy)phenyl]amine



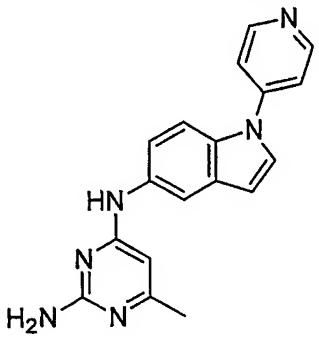
The product was prepared using a similar method used for the preparation of Example 43 (described above) from A21 and B11: HPLC/MS: $[M+H]^+$ 382.1 *m/z*. Retention time (HPLC/MS) = 2.91 min.

Examples 47-49

Using procedures similar to the above examples and using the appropriate Intermediates A and B, the following examples were prepared in like manner:

Example 47

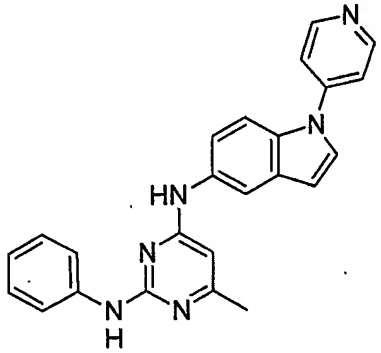
Preparation of *N*-(2-amino-6-methyl-4-pyrimidinyl)-*N*-[1-(4-pyridinyl)-1*H*-indol-5-yl]amine



Prepared by reaction of Intermediate A7 and B1.

Example 48

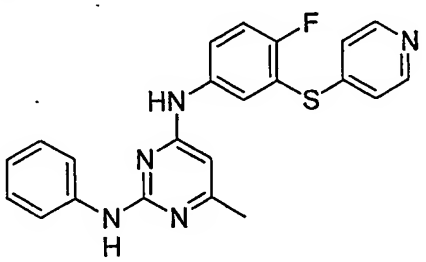
Preparation of *N*-(2-anilino-6-methyl-4-pyrimidinyl)-*N*-[1-(4-pyridinyl)-1H-indol-5-yl]amine



Prepared by reaction of Intermediate A16 and B1.

Example 49

Preparation of *N*-(2-anilino-6-methyl-4-pyrimidinyl)-*N*-[4-fluoro-3-(4-pyridinylsulfanyl)phenyl]amine



Prepared by reaction of Intermediate A16 and B7.

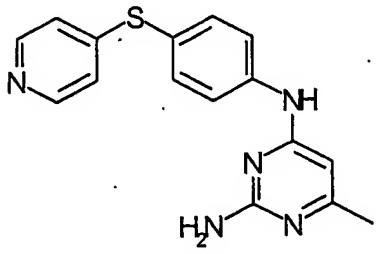
Rho Kinase Biochemical Assay:

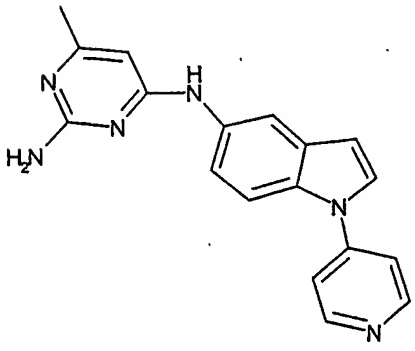
ROCK-1 activity criteria: 0 no effect (< 40% inhibition), 1 effect (> 40% inhibition). The assay tests for inhibition of ROCK-1 phosphorylation of MBP (Myelin Basic Protein). The reaction (100 µl final volume) is carried out in polypropylene 96-well plates in 50 mM HEPES buffer pH 7.5 containing 5 mM $MgCl_2$ and 1 mM DTT. For each well, gstROCK1 (0.25 µgs of BAYER DRT gstROCK1) is combined with MBP (1 µg) in reaction buffer (70 µL combined volume). Inhibitors (5 µL of 20x conc. in 40% DMSO) are added to each well to give an 8 point dose response range from 1.0 µM to .5 nM. The reaction is begun by adding 25 µL of ATP (4x = 12 µM) in reaction buffer containing 0.8 µCi of ^{33}P gamma-ATP (4x) for a final concentration of 3 µM cold and 0.2 µCi hot ATP. Plates were incubated for 1 hour at room temperature with the reaction being stopped by addition of 7 µL of 1 N HCl. The radioactively labeled MBP was transferred to P30 filtermats (EG&G Wallac), washed in 1% phosphoric acid followed by brief washes in water. The filtermats were then dried and the incorporation of ^{33}P detected by liquid scintillation counting. Background ^{33}P incorporation is determined by ROCK1 autophosphorylation without MBP. The data are expressed as percent inhibition: % inhibition = 1-((cpm with inhibitor-background)/(cpm without inhibitor - background)) * 100.

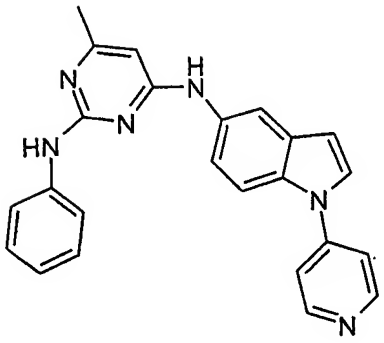
The entire disclosure of all applications, patents and publications, cited herein and of U.S. Provisional Application Serial No. 60/349,986, filed January 23, 2002 is incorporated by reference herein.

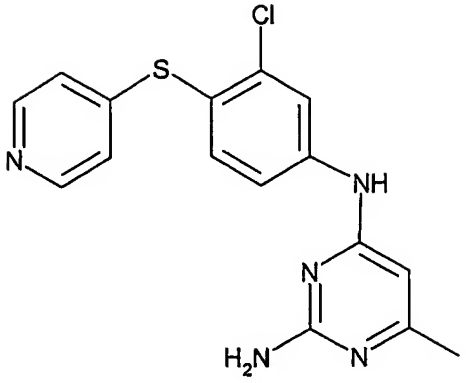
WE CLAIM:

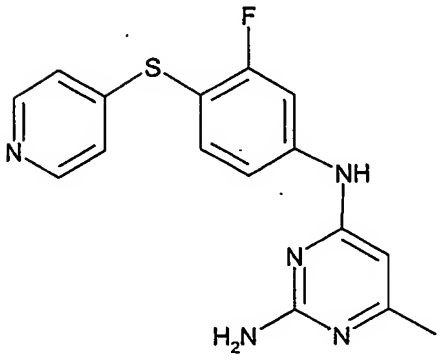
1. A compound of the formula

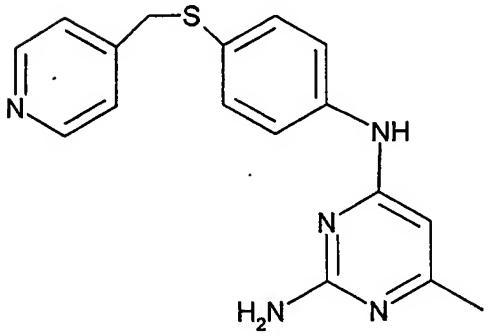


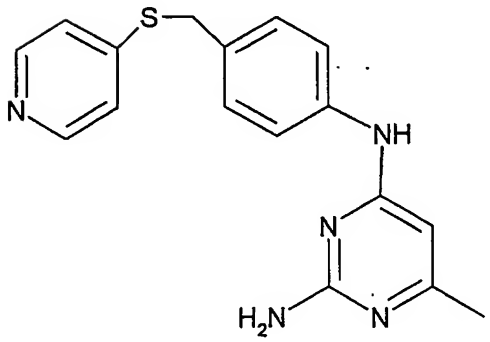


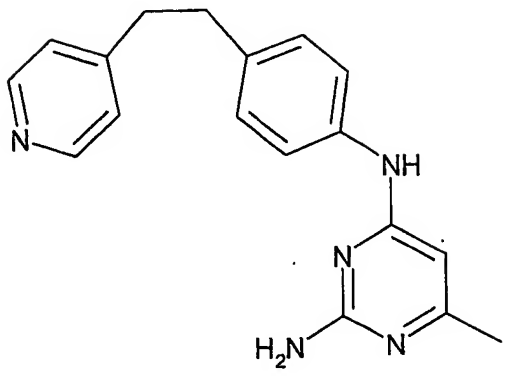


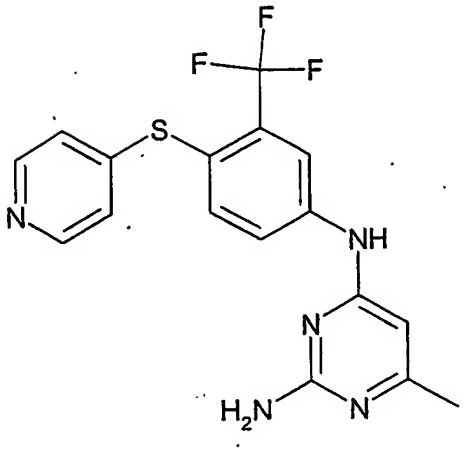


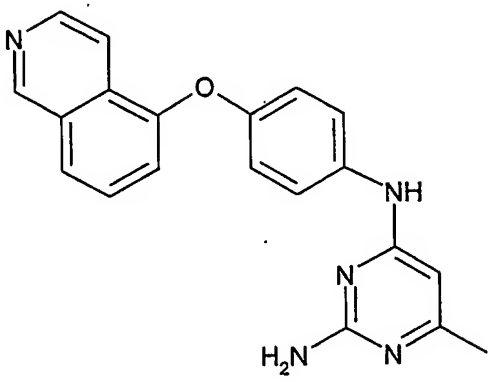


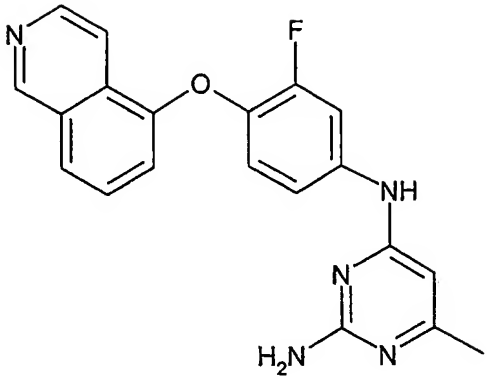


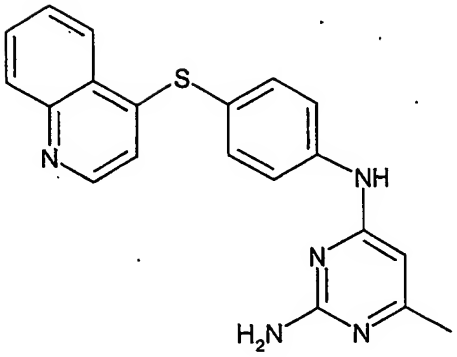


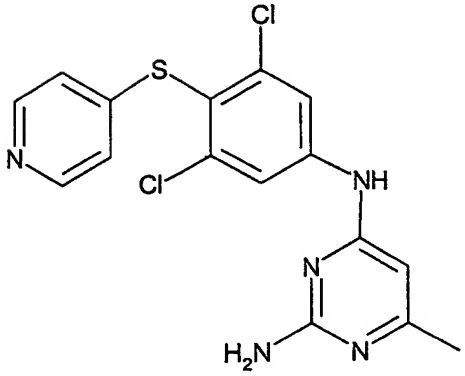


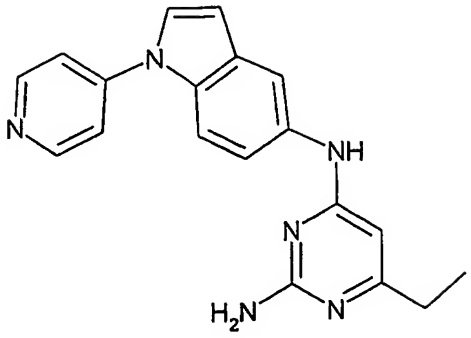


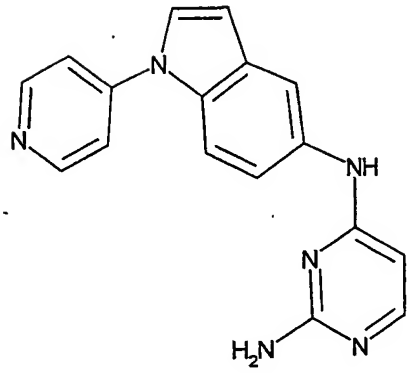


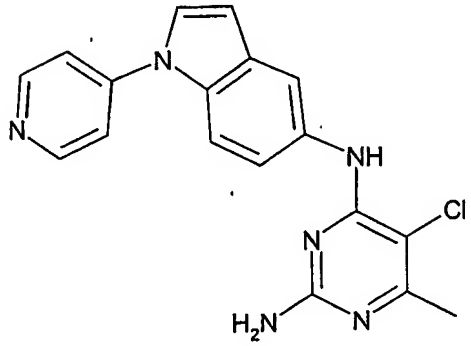


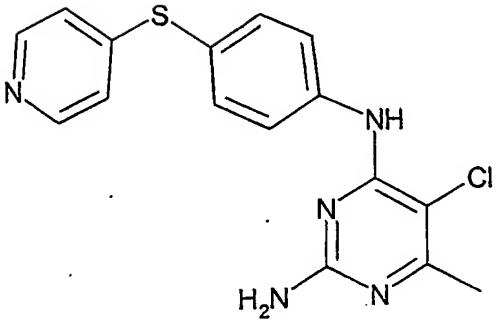


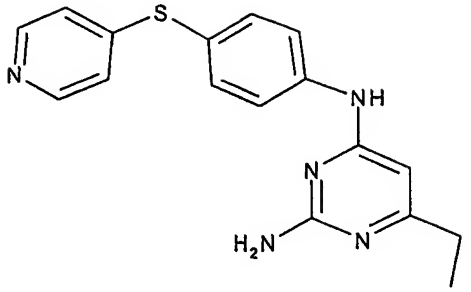


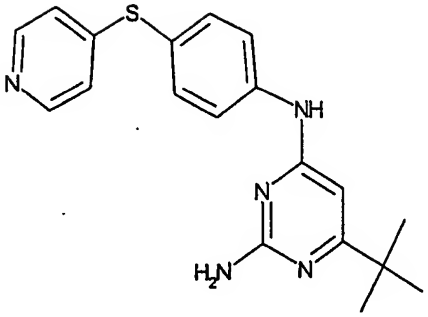


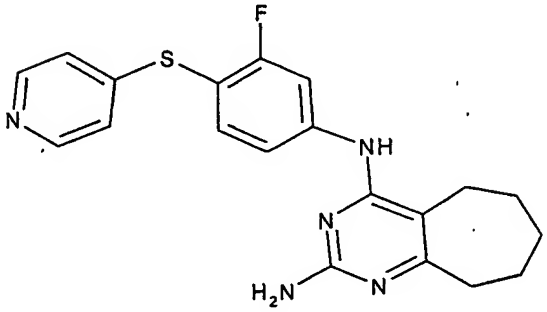


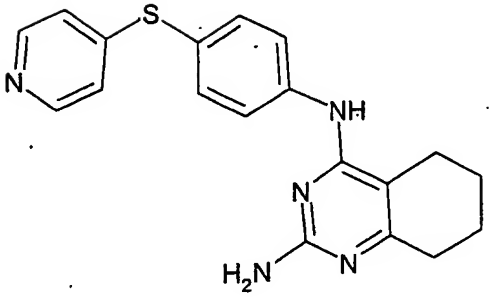


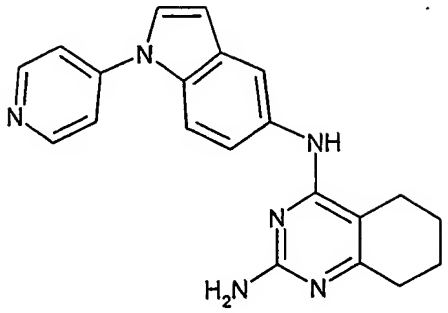


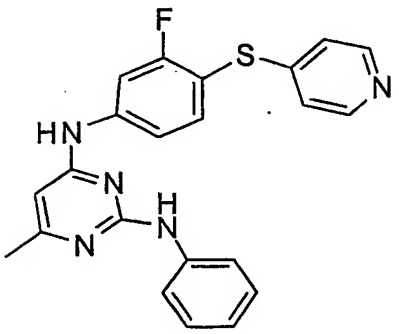


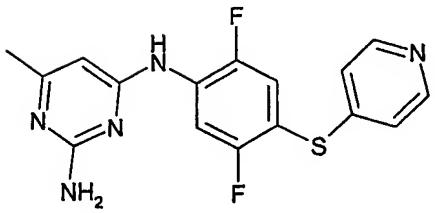


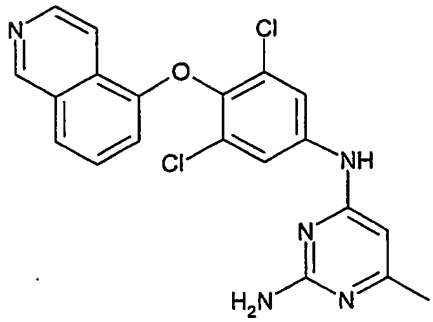


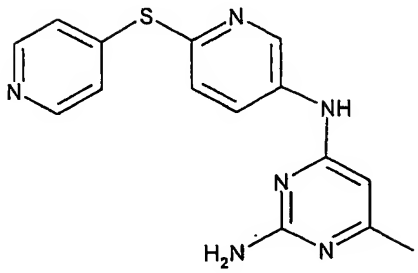


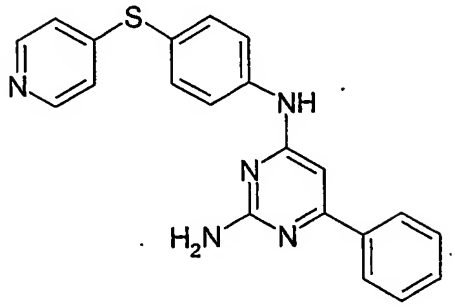


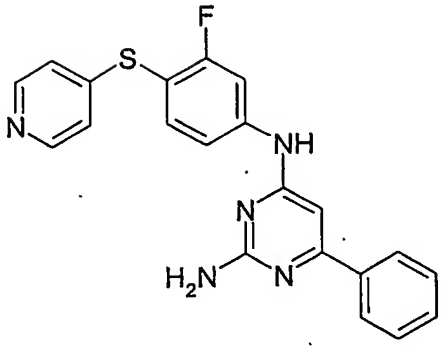


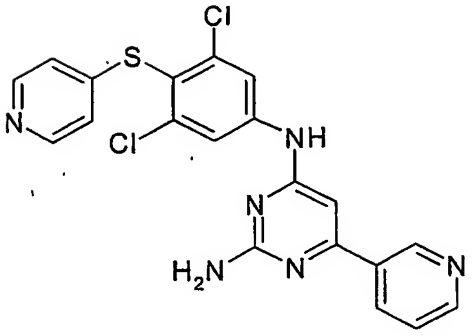


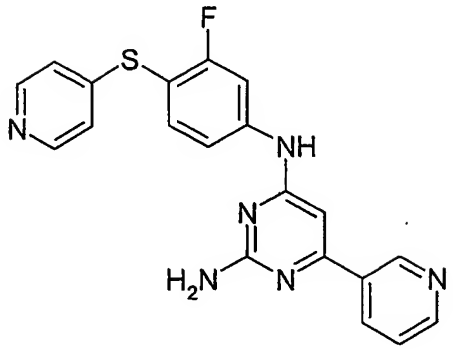


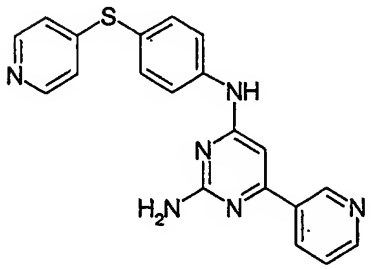


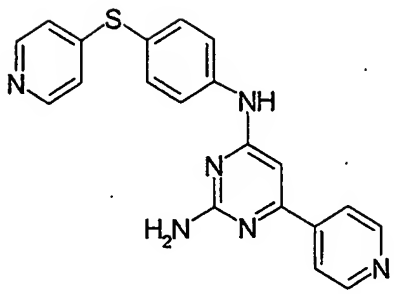


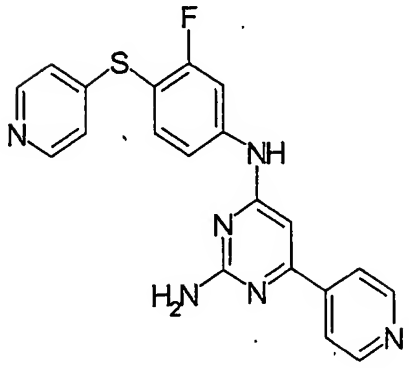


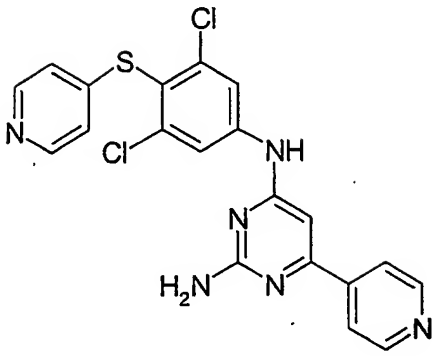


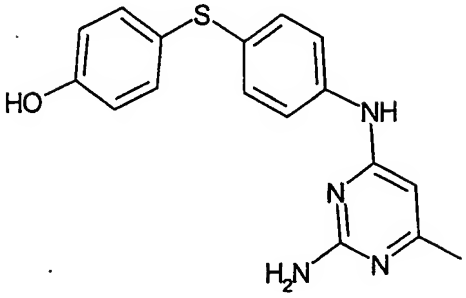


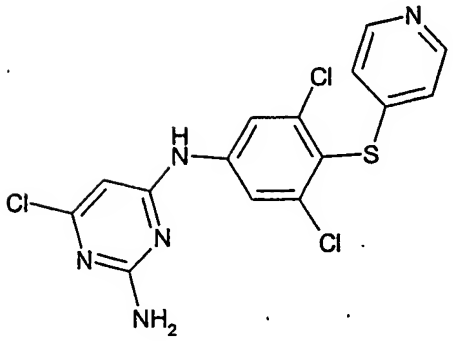


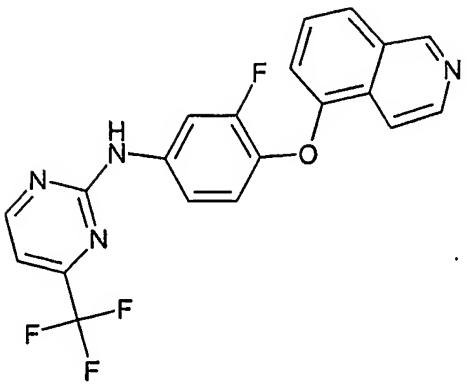


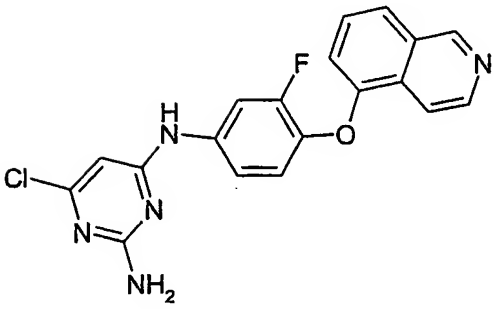


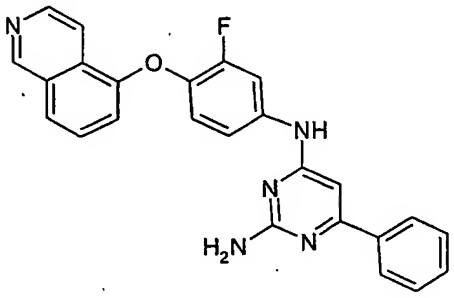


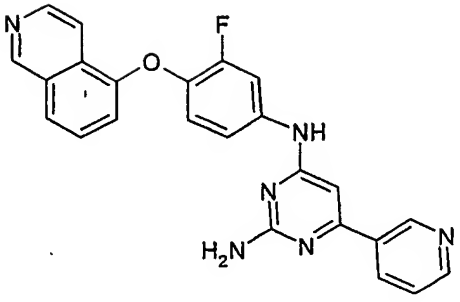


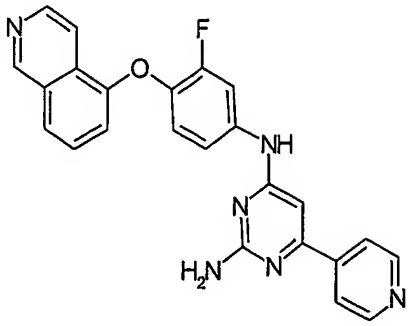


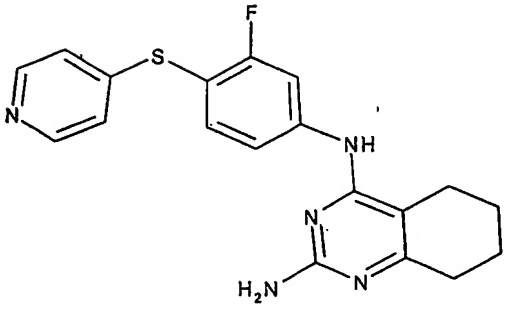


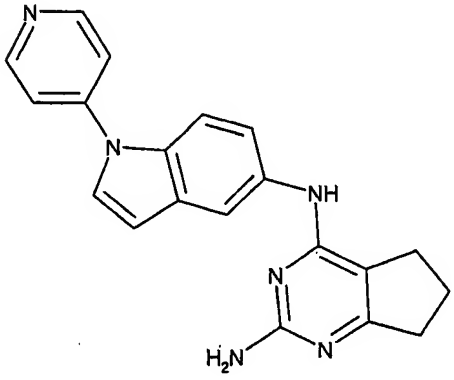


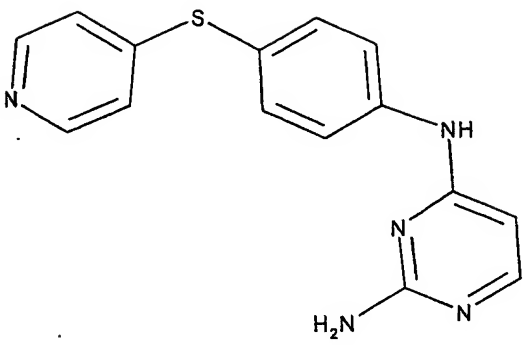


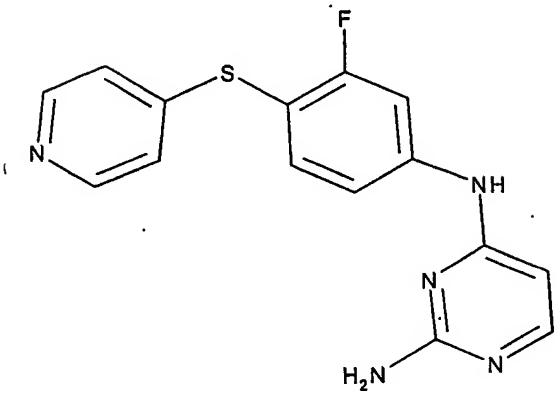


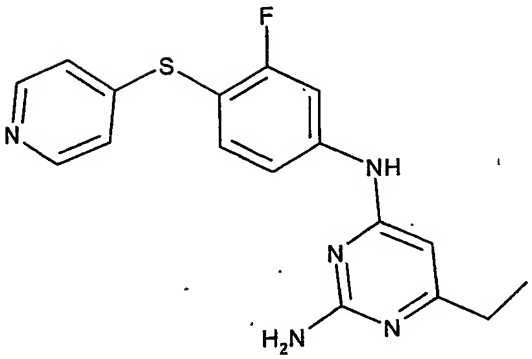




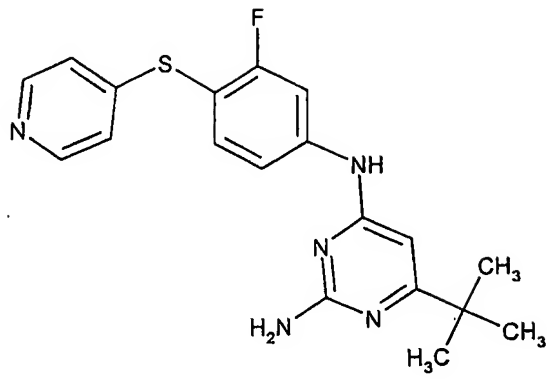








or



2. A method of treating an indication mediated by Rho-kinase, comprising administering a compound of claim 1.

3. A process according to claim 1, wherein the host is a human.

4. A method of treating hypertension, atherosclerosis, restenosis, cerebral ischemia, cerebral vasospasm, neuronal degeneration, spinal cord injury, cancer of the breast, colon, prostate, ovaries, brain or lung, thrombotic disorders, asthma, glaucoma, osteoporosis or erectile dysfunction, comprising administering to host in need thereof a compound according to claim 1.

5. A process according to claim 4, wherein the host is a human.

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 03/01840

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D401/12 A61K31/506 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 28561 A (MERCK) 26 April 2001 (2001-04-26) page 0; claims; table 1	1-3
A	WO 00 39101 A (ASTRAZENECA) 6 July 2000 (2000-07-06) page 0; claims; example 78	1-5

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2003	25/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 117, no. 25, 1992 Columbus, Ohio, US; abstract no. 251318p, M. BADRAN ET AL.: "NOVEL PIPERAZINYL-SUBSTITUTED PYRIMIDINES AS ANTIHYPERTENSIVE A. VASODILATATORS." page 688; XP002243213 abstract & REV. ROUM. DE CHIM., vol. 37, no. 2, 1992, pages 283-8, ROMANIA	1,4

INTERNATIONAL SEARCH REPORT

Inten al application No.
PCT/US 03/01840

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 2 to 5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/US 03/01840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0128561 A	26-04-2001	AU 1212501 A	30-04-2001
		WO 0128561 A1	26-04-2001
WO 0039101 A	06-07-2000	AU 1874300 A	31-07-2000
		BR 9916590 A	23-10-2001
		CA 2352896 A1	06-07-2000
		CN 1335838 T	13-02-2002
		EP 1140860 A1	10-10-2001
		WO 0039101 A1	06-07-2000
		JP 2002533446 T	08-10-2002
		NO 20013038 A	22-08-2001